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Organotins in drinking-water

Background document for development of WHO *Guidelines for drinking-water quality*

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Preface

Access to safe drinking-water is essential to health, a basic human right and a component of effective policy for health protection. A major World Health Organization (WHO) function to support access to safe drinking-water is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters ...", including those related to the safety and management of drinking-water.

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International standards for drinking-water*. It was revised in 1963 and 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for drinking-water quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects, reviewing selected microorganisms, was published in 2002. The third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2006, and the second addendum to the third edition was published in 2008. The fourth edition was published in 2011, and the first addendum to the fourth edition was published in 2017.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation relating to aspects of protection and control of drinking-water quality is accordingly prepared and updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other information to support the GDWQ, describing the approaches used in deriving guideline values, and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a background document evaluating the risks to human health from exposure to that chemical in drinking-water was prepared. The draft health criteria document was submitted to a number of scientific institutions and selected experts for peer review. The draft document was also released to the public domain for comment. Comments were carefully considered and addressed, as appropriate, taking into consideration the processes outlined in the *Policies and procedures used in updating the WHO guidelines for drinking-water quality* and the WHO *Handbook for guideline development*. The revised draft was submitted for final evaluation at expert consultations.

During preparation of background documents and at expert consultations, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents; the International Agency for Research on Cancer; the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Meeting on Pesticide Residues; and the Joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO website and in the current edition of the GDWQ.

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The work of the following experts was crucial in the development of this document and others in the second addendum to the fourth edition:

Dr M Asami, National Institute of Public Health, Japan
Dr RJ Bevan, independent consultant, United Kingdom
Mr R Carrier, Health Canada, Canada
Dr J Cotruvo, Joseph Cotruvo & Associates and NSF International WHO Collaborating Centre, United States of America
Dr D Cunliffe, South Australia Department of Health, Australia
Dr A Eckhardt, Umweltbundesamt (Federal Environment Agency), Germany
Professor JK Fawell, Cranfield University, United Kingdom
Dr A Hirose, National Institute of Health Sciences of Japan
Dr A Humpage, University of Adelaide (formerly South Australian Water Corporation), Australia
Dr P Marsden, Drinking Water Inspectorate, United Kingdom
Professor Y Matsui, Hokkaido University, Japan
Dr E Ohanian, Environmental Protection Agency, United States of America
Professor CN Ong, National University of Singapore, Singapore
Dr J Strong, Environmental Protection Agency, United States of America
Dr E Testai, National Institute of Health, Italy

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Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document are greatly appreciated.

Acronyms and abbreviations

BMD	benchmark dose
$BMDL_{10}$	lower 95% confidence limit on the benchmark dose for a 10% response
bw	body weight
CPVC	chlorinated polyvinyl chloride
DBT	dibutyltin
DBTA	dibutyltin diacetate
DBTC	dibutyltin dichloride
DBTO	dibutyltin oxide
DET	diethyltin
DMT	dimethyltin
DMTC	dimethyltin dichloride
DNA	deoxyribonucleic acid
DOT	di-*n*-octyltin
DOTC	dioctyltin dichloride
DOTO	dioctyltin oxide
DOTTG	dioctyltin diisothioglycolate
DPT	diphenyltin
DPTC	diphenyltin dichloride
EFSA	European Food Safety Authority
GD	gestation day
GDWQ	*Guidelines for drinking-water quality*
GV	guideline value
HBV	health-based value
HGPRT	hypoxanthine–guanine phosphoribosyltransferase
IgG	immunoglobulin G
IgM	immunoglobulin M
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MBT	monobutyltin
MBTC	monobutyltin trichloride
MBTO	monobutyltin oxide
METC	monoethyltin trichloride
MMT	monomethyltin
MMTC	monomethyltin trichloride
MOT	mono-*n*-octyltin
MOTC	monooctyltin trichloride
MOTTG	monooctyltin triisooctylthioglycolate
MPT	monophenyltin
MPTC	monophenyltin trichloride
NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
PND	postnatal day
PVC	polyvinyl chloride

TBT	tributyltin
TBTC	tributyltin chloride
TBTO	tributyltin oxide
TDI	tolerable daily intake
TeBT	tetrabutyltin
TeET	tetraethyltin
TeOT	tetraoctyltin
TePT	tetraphenyltin
TET	triethyltin
TG	Test Guideline
TMT	trimethyltin
TMTC	trimethyltin chloride
TOT	trioctyltin
TPT	triphenyltin
TPTA	triphenyltin acetate
TPTC	triphenyltin chloride
TPTO	triphenyltin oxide
TPTOH	triphenyltin hydroxide
USA	United States of America
WHO	World Health Organization

Contents

Much of the information in this background document has been taken from reviews by the European Food Safety Authority (EFSA, 2004), the Organisation for Economic Co-operation and Development (OECD, 2008a,b, 2009a–f, 2010) and the International Programme on Chemical Safety (IPCS, 2006). Critical new information published since the publication of these reviews has been obtained from a search of the publicly available scientific literature.

Executive summary

The organotins are a large class of compounds that differ in their properties and applications. This background document deals with monosubstituted, disubstituted, trisubstituted and tetrasubstituted alkyltins and phenyltins, including their chloride forms. This is because, after ingestion, organotins may be converted to, and absorbed as, their chlorides in the gastrointestinal tract.

The critical end-point for the risk assessment of trisubstituted and disubstituted compounds is immunotoxicity. In the absence of specific studies on combined effects, the immunotoxic effects of these compounds were considered additive. Based on chronic immunotoxicity studies in rats, a tolerable daily intake (TDI) of 0.25 µg/kg body weight (bw) (0.1µg/kg bw as tin) was established by applying an uncertainty factor of 100 to the no-observed-adverse-effect level for tributyltin oxide, the reference organotin, for assessing combined exposure to tributyltin, dibutyltin, triphenyltin and diocytltin. Allocating 20% of the group TDI of 0.25 µg/kg bw to drinking-water and assuming that a 60 kg person consumes 2 L of drinking-water per day, a health-based value (HBV) of 1.5 µg/L (equivalent to 0.6 µg/L as tin) can be derived for the sum of these organotins.

Recognizing the lack of standard data on chronic intake to derive a reliable lifetime TDI value for monomethyltin or dimethyltin, the lowest exposures (around 1 mg/kg bw/day) associated with adverse effects were one order of magnitude higher than dose levels associated with immunotoxicity of tributyltin oxide. Because these organotins would normally be found in drinking-water as a result of their use as stabilizers in polyvinvyl chloride (PVC) and chlorinated polyvinvyl chloride (CPVC), where their use is normally controlled by product specification, there is no need to establish a guideline value (GV) for them. Current knowledge is inadequate for setting an HBV or GV for other organotins.

Many methods are available for analysing organotin compounds in source water. It is important to control both organotins that are present in the source water as environmental contaminants and organotins that leach from PVC piping; the latter should be controlled by product specification. The removal efficiency of organotins by water treatment appears to be significantly different for different compounds.

1 General description

1.1 Identity

The organotins are a large class of compounds that differ in their properties and applications. They can be divided into four groups with the general formulas R_4Sn, R_3SnX, R_2SnX_2 and $RSnX_3$, where R is usually an organic group and X is an anion (e.g. chloride, fluoride, oxide, hydroxide). When the compounds are used as heat stabilizers, the alkyl group can be methyl, butyl, octyl or dodecyl. The most common are produced by the reaction of monoalkyltin and dialkyltin chlorides with mercaptoesters to give thioglycolates.

This background document deals with monosubstituted, disubstituted, trisubstituted and tetrasubstituted alkyltins and phenyltins.

1.2 Physicochemical properties

Some physicochemical properties of organotin compounds are shown in Table 1.1.

Table 1.1. Physicochemical properties of organotins (as chloride)

Organotin	Chemical formula	CAS No.	MW (g/mol)	Melting/ freezing point (°C)	Boiling point (°C)	Water solubility (g/L)	Vapour pressure (Pa) at 25 °C	Log K_{ow}
TMTC*	$(CH_3)_3ClSn$	1066-45-1	199.3	37.5	154–156	Miscible	No data	No data
DMTC	$(CH_3)_2Cl_2Sn$	753-73-1	219.7	90	188–190 at 1013.3 hPa	823 at 20 °C	25	−2.18
MMTC	CH_3Cl_3Sn	993-16-8	240.1	43	171 at 1013.3 hPa	1038 at 20 °C	170	−0.9
TeBT	$(C_4H_9)_4Sn$	1461-25-2	347.2	<−20	196.9 at 1013.3 hPa	<0.0001 at 20 °C	0.14−0.26	9.37
TBTC	$(C_4H_9)_3ClSn$	1461-22-9	325.5	−18	264–275 at 1013.3 hPa	6–10 at 21 °C	1.6–2.8	2.07
DBTC	$(C_4H_9)_2Cl_2Sn$	683-18-1	303.8	42	114 at 80 hPa	0.32 at 20 °C	0.16	0.97
MBTC	$C_4H_9Cl_3Sn$	1118-46-3	282.2	−63	98 at 13 hPa	Miscible	6	0.18
TeOT	$(C_8H_{17})_4Sn$	3590-84-9	571.6	−102	414–425 at 1013.3 hPa	<0.0001	940	17.2
TOTC	$(C_8H_{17})_3ClSn$	2587-76-0	493.8	No data	No data	No data	No data	No data
DOTC	$(C_8H_{17})_2Cl_2Sn$	3542-36-7	416.1	45–47	175 at 1.3 hPa	0.00024–0.00028	516	5.8
MOTC	$C_8H_{17}Cl_3Sn$	3091-25-6	338.3	<10	150–159 at 13 hPa	0.00033	0.5	2.1
TePT**	$(C_6H_5)_4Sn$	595-90-4	427.1	228	420	No data	1226.6	8.34
TPTC*	$(C_6H_5)_3ClSn$	639-58-7	385.5	103.5	240 at 19 hPa	0.04 at 20 °C	No data	4.19
DPTC**	$(C_6H_5)_2Cl_2Sn$	1135-99-5	343.8	42	335	0.05 at 20 °C	1202.6	1.38
MPTC**	$C_6H_5Cl_3Sn$	1124-19-2	302.2	No data	No data	13.9 at 25 °C	36.9	−0.08

CAS: Chemical Abstracts Service; DBTC: dibutyltin dichloride; DMTC: dimethyltin dichloride; DOTC: dioctyltin dichloride; DPTC: diphenyltin dichloride; MBTC: monobutyltin trichloride; MMTC: monomethyltin trichloride; MOTC: monooctyltin trichloride; MPTC: monophenyltin trichloride; MW: molecular weight; TBTC: tributyltin chloride; TeBT: tetrabutyltin; TeOT: tetraoctyltin; TePT: tetraphenyltin; TMTC: trimethyltin chloride; TOTC: trioctyltin chloride; TPTC: triphenyltin chloride

Source: Physicochemical properties are derived from SIDS initial assessment reports (OECD, 2008a,b, 2009a–f, 2010). Data marked with an asterisk (*) are from ATSDR (2005), and data marked with ** are from ChemIDplus (http://chem.sis.nlm.nih.gov/chemidplus/).

1.3 Organoleptic properties

No information was found regarding taste or odour thresholds for organotin compounds in water.

1.4 Major uses and sources

Monoalkyltins and dialkyltins are generally used in mixtures in various amounts as heat stabilizers in the manufacture of polyvinyl chlorine (PVC) and chlorinated polyvinyl chloride (CPVC) plastics. Dialkyltins have also been approved as PVC stabilizers for materials in contact with food and water (EFSA, 2004). Some monoalkyltins and dialkyltins are also used in depositing clear, durable tin oxide coatings on reusable glass bottles. Dialkyltins are used as catalysts in producing various polymers and esters, and also as stabilizers for lubricating oils, hydrogen peroxide and polyolefins (Environment Canada & Health Canada, 2009).

Trialkyltins and triphenyltins have been used extensively as timber preservatives; as fungicides in crops including potatoes, sugar beets and pecans; in antifouling paints for boats; and as pesticides (EFSA, 2004). Diphenyltins (DPTs) are generated by the degradation of triphenyltin (TPT) through biological, ultraviolet irradiation, chemical or thermal mechanisms (IPCS, 1999a). Controls introduced globally since the 1980s over the use of tributyltin (TBT) or TPT in antifouling paints on vessels are expected to result in a significant decrease in the amount of these contaminants entering the environment.

Trialkyltins occur as contaminants in other commercial organotin products (Environment Canada & Health Canada, 2009). For example, TBT can be an impurity at concentrations of up to about 20% in tetrabutyltin (TeBT) imported for use in the synthesis of organotin stabilizers, and is present at lower concentrations (up to about 0.5%) in commercial dibutyltin (DBT) products (Environment Canada, 2006).

TeBT is used as an industrial intermediate in the production of butyltin chemicals, and may be sold to other chemical or industrial manufacturers for conversion to other products; releases to the environment could occur as part of the production of intermediates, or during its conversion to other butyltin chemicals (OECD, 2009e). Tetraoctylin (TeOT) is only used as an industrial intermediate in the synthesis of other octyltin compounds; releases to the environment could occur via losses during production of this intermediate, or during its conversion to other octyltin chemicals (OECD, 2009f).

1.5 Environmental fate

Releases of organotin compounds to air from various surfaces are, in general, not significant, because of their low vapour pressures (Fent, 1996). Organotin compounds are generally only sparingly soluble in water, and are likely to partition to soils and sediments (ATSDR, 2005). As the range of both the water solubilities and the log octanol–water partition coefficients of organotin compounds is very wide (as shown in Table 1.1), some organotin compounds may partition from water to aquatic organisms. In addition, environmental degradation of organotin compounds with the dissociation of the carbon–tin bond, as described below, may change the environmental mobility of the compounds. Therefore, the overall kinetics of the environmental fate of the organotin compounds seems to be complex.

The carbon–tin bond of organotin compounds is relatively stable, compared with the hydrolysis of the anionic substituent (e.g. an isooctyl mercaptoacetate group). In water, most derivatives are reported to dissociate to the constituent alkyltin (usually as the chloride or the oxide) and the relevant anion (KemI, 2000). Results of the Organisation for Economic Co-operation and Development (OECD) respiration inhibition test (OECD Test Guideline 301F) indicated that the organotins were readily biodegradable. However, there is some doubt about whether this reflects full degradation or hydrolysis of the anionic substituent (IPCS, 2006).

Degradation of tributyltin oxide (TBTO) involves the dissociation of the carbon–tin bond (IPCS, 1990). This can result from various processes (both physicochemical and biological reactions) occurring simultaneously in the environment. Dealkylation of organotin compounds occurs under conditions of extreme pH, and is barely evident under normal environmental conditions.

TeBT and TeOT are stable in water as a result of a lack of hydrolysable functional groups, and not readily biodegradable. However, they are expected to be degraded by reaction with photochemically produced hydroxyl radical in the atmosphere (OECD, 2009e,f).

Photodegradation occurs during laboratory exposures of solutions to ultraviolet light at 300 nm (and to a lesser extent at 350 nm). Under natural conditions, photolysis is limited by the wavelength range of sunlight and by the limited penetration of ultraviolet light into water (IPCS, 1999b). Soderquist & Crosby (1980) reported that exposure of TPT in water to sunlight resulted in a half-life of approximately 18 days. For the purposes of environmental modelling using the European Union System for the Evaluation of Substances programme, the half-lives of photodegradation for dialkyltins and monoalkyltins range from 0.4 days (dioctyltin chloride [DOTC]) to 64 days (monomethyltin chloride [MMTC]) (IPCS, 2006).

Biodegradation depends on environmental conditions such as temperature, oxygenation, pH, the level of mineral elements, the presence of easily biodegradable organic substances for co-metabolism, and the nature of the microflora and its capacity for adaptation. As with abiotic degradation, biotic breakdown of TBT is a progressive oxidative debutylization involving the splitting of the carbon–tin bond. DBT derivatives are more readily degraded than TBT (IPCS, 1999b). It is generally accepted that biodegradation half-lives are longer in both seawater and soil/sediment than in fresh water. A field study of the degradation of methyltin and butyltin compounds in a forest floor, a mineral and a wetland soil with incubation experiments at 20 °C in the dark found half-lives ranging from 0.5 to 15 years. Degradation rates were generally in the order monosubstituted ≥ disubstituted > trisubstituted organotins (Huang & Matzner, 2004). Measured half-lives of dialkyltins in soils, as determined from sampling in lysimeters, are around 120–150 days in laboratory tests (Terytze, Schwarz & Kaiser, 2000). Decomposition rates were higher in organic forest soils than in wetland and mineral soils (Huang & Matzner, 2004).

For risk assessment purposes, exposure modelling is often done using the precautionary assumption that the compounds are inherently degradable, with a default half-life of 150 days (IPCS, 2006).

2 Environmental levels and human exposure

2.1 Air

Unknown quantities of organotins may be released into air from factories that produce polyurethane or PVC resins in which organotins are used as stabilizers. However, there appear to be no analytical data to support this assumption.

2.2 Water

Organotins can leach into surface water from treated timber or antifouling paints used on boats, or into drinking-water from PVC and CPVC pipes where organotins are used as stabilizers. Organotin concentrations in various water bodies are shown in Table 2.1.

Table 2.1. Organotin concentrations in various water bodies

Compound	Concentration	Notes	Reference
DMT	400 ng/L as Sn	Fresh water	Summer, Klein & Griem (2003)
MMT	1200 ng/L as Sn	Fresh water	Summer, Klein & Griem (2003)
TBT	3620 ng/L as Sn	Rivers and lakes	Hoch (2001)
	<2–200 ng/L as TBTO (<0.4–40 ng/L as Sn)	Rivers in Japan	Tsuda & Kagatsume (2005)
	<2–3 ng/L as TBTO（<0.4–0.6 ng/L as Sn)	Lakes in Japan	Tsuda & Kagatsume (2005)
	<0.5–10 ng/L as Sn	Rivers in China	Jiang et al. (2001)
	0.5–37.6 ng/L as Sn	Lakes in China	Jiang et al. (2001)
	<0.5 ng/L as Sn	Rivers in Canada	Chau et al. (1997); Yang, Maguire & Chau (2001)
	<0.5–9.6 ng/L as Sn	Lakes in Canada	Chau et al. (1997); Yang, Maguire & Chau (2001)
	<2–13 ng/L (<0.8–5.3 ng/L as Sn)	Switzerland	Fent & Hunn (1995)
	3 ng/L as Sn (mean)	Germany	Shawky & Emons (1998)
TeBT	Not detected to 151.4 ng/L as TeBT (Not detected = 0.5–1.0 ng/L as TeBT)	USA	Parametrix (1994a,b, 1995, 1996, 1997, 1998, 1999, 2001)

Compound	Concentration	Notes	Reference
DBT	3700 ng/L as Sn (mean = 148 ng/L as Sn; median = 25 ng/L as Sn)	Fresh water in Canada	Environment Canada & Health and Welfare Canada (1993)
	15 700 ng/L as Sn	Fresh water in India	Summer, Klein & Griem (2003)
	101 ng/L as Sn	Rivers in India	Ansari, Singh & Tobschall (1998)
	<1.5–3.1 ng/L as Sn	Rivers in China	Jiang et al. (2001)
	<1.5–95.2 ng/L as Sn	Lakes in China	Jiang et al. (2001)
	<0.5 ng/L as Sn	Rivers in Canada	Chau et al. (1997); Yang, Maguire & Chau (2001)
	<0.3–0.5 ng/L as Sn	Lakes in Canada	Chau et al. (1997); Yang, Maguire & Chau (2001)
	2–18 ng/L (1.0–9.2 ng/L as Sn)	Switzerland	Fent & Hunn (1995)
	23 ng/L (mean = 11.7 ng/L as Sn)	Germany	Shawky & Emons (1998)
MBT	1900 ng/L as Sn	Fresh water in India	Summer, Klein & Griem (2003)
	70 ng/L as Sn	Rivers in India	Ansari, Singh & Tobschall (1998)
	<28–132.3 ng/L as Sn	Rivers in China	Jiang et al. (2001)
	<28–312.5 ng/L as Sn	Lakes in China	Jiang et al. (2001)
	<0.5 ng/L as Sn	Rivers in Canada	Chau et al. (1997); Yang, Maguire & Chau (2001)
	<0.3–2.9 ng/L as Sn	Lakes in Canada	Chau et al. (1997); Yang, Maguire & Chau (2001)
	5700 ng/L as Sn (mean = 216 ng/L as Sn; median = 27 ng/L as Sn)	Fresh water in Canada	Environment Canada & Health and Welfare Canada (1993)
	2–12 ng/L (1.4–8.2 ng/L as Sn)	Switzerland	Fent & Hunn (1995)
	15 ng/L (mean = 10.2 ng/L as Sn)	Germany	Shawky & Emons (1998)
DOT	Not detected in biota or any environmental medium	Canada (LOD 10 ng/L)	Environment Canada & Health and Welfare Canada (1993)
	0–5 ng/L as Sn	11 rivers in France	Bancon-Montigny, Lespes & Potin-Gautier (2004)
MOT	Not detected in biota or any environmental medium	Canada (LOD 10 ng/L as Sn)	Environment Canada & Health and Welfare Canada (1993)
	0–5 ng/L as Sn	11 rivers in France	Bancon-Montigny, Lespes & Potin-Gautier (2004)
TOT	0–5 ng/L as Sn	11 rivers in France	Bancon-Montigny, Lespes & Potin-Gautier (2004)

Compound	Concentration	Notes	Reference
TPT	600 ng/L (245.5 ng/L as Sn)	Fresh water in the USA, detected in two sites	Jones-Lepp, Varner & Heggem (2004)
	7 ng/L as Sn	French non-boating rivers	Bancon-Montigny, Lespes & Potin-Gautier (2004)
	<5–7 ng/L (<1.7–2.4 ng/L as Sn)	Switzerland	Fent & Hunn (1995)
	<4–80 ng/L as TPT (<1.4–27.2 ng/L as Sn)	Lakes in Switzerland	Fent & Hunn (1995)
TPTC	<1–6 ng/L (<0.3–0.8 ng/L as Sn)	Rivers in Japan	Tsuda & Kagatsume (2005)
	<1–1 ng/L (<0.34–0.34 ng/L as Sn)	Lakes in Japan	Tsuda & Kagatsume (2005)
DPT	14 ng/L as Sn	French non-boating rivers	Bancon-Montigny, Lespes & Potin-Gautier (2004)
	<4 ng/L as DPT (<1.7 ng/L as Sn)	Rivers in Switzerland	Fent & Hunn (1995)
	<3–20 ng/L as DPT (<1.3–8.6 ng/L as Sn)	Lakes in Switzerland	Fent & Hunn (1995)
MPT	722 ng/L as Sn	French non-boating rivers	Bancon-Montigny, Lespes & Potin-Gautier (2004)
	<4 ng/L (<2.4 ng/L as Sn)	Rivers in Switzerland	Fent & Hunn (1995)
	<2–30 ng/L as MPT (<1.2–18.3 ng/L as Sn)	Lakes in Switzerland	Fent & Hunn (1995)
	400–700 ng/L as Sn	Industrial or agricultural sites in south-west France	ATSDR (2005)

DBT: dibutyltin; DMT: dimethyltin; DOT: dioctyltin; DPT: diphenyltin; LOD: limit of detection; MBT: monobutyltin; MMT: monomethyltin; MOT: monooctyltin; MPT: monophenyltin; TBT: tributyltin; TBTO: tributyltin oxide; TeBT: tetrabutyltin; TOT: trioctyltin; TPT: triphenyltin; TPTC: triphenyltin chloride

Organotin stabilizers leach into drinking-water from plastic pipes, although usually at very low concentrations, as shown in Table 2.2.

Table 2.2. Organotin concentrations in drinking-water

Compound	Concentration	Notes	Reference
MMT	0.5–6.5 ng/L (as Sn)	Canada	Sadiki et al. (1996)
	<0.5–290.6 ng/L (as Sn)	Canada (winter–spring)	Sadiki & Williams (1999)
	0.49–8.1 ng/L (as Sn)	Florida, USA	Braman & Tompkins (1979)
DMT	0.5–257 ng/L (as Sn)	Canada	Sadiki et al. (1996)
	<0.5–49.1 ng/L (as Sn)	Canada (winter–spring)	Sadiki & Williams (1999)
	0.40–2.2 ng/L (as Sn)	Florida, USA	Braman & Tompkins (1979)
MBT	ng/L range (unspecified)	Canada	Forsyth & Jay (1997)
	28.5 ng/L (maximum)	Canada	Sadiki & Williams (1999)
DBT	100 µg/L	DBT sulfide; static water	Mazaev & Slepnina (1973)
	ng/L range (not further specified)	Canada	Forsyth & Jay (1997)
	53 ng/L (maximum)	Canada	Sadiki & Williams (1999)
TBT	32.1 ng/L (maximum; as Sn)	Northern China	Gao et al. (2009)
TPT	41.3 ng/L (maximum; as Sn)	Northern China	Gao et al. (2009)
Mixture (MBT, DBT, TBT, MPT, DPT and TPT)	Not detected to 142.4 ng/L (as Sn)	Northern China	Gao et al. (2009)

DBT: dibutyltin; DMT: dimethyltin; DPT: diphenyltin; MBT: monobutyltin; MMT: monomethyltin; MPT: monophenyltin; TBT: tributyltin; TPT: triphenyltin

2.3 Food

Mean and median concentrations of various organotins in European fishery and seafood products are shown in Table 2.3.

Table 2.3. Organotin concentrations in European fishery and seafood products

	Concentration (µg/kg)			
	Fishery products		Seafood products (other than fish)	
Organotin	Mean (median)	Minimum–maximum	Mean (median)	Minimum–maximum
TBT	28.4 (7.0)	0.2–1 830	60.3 (14.0)	2.0–1 830
DBT	16.8 (2.5)	0.1–1 400	52.4 (4.0)	0.5–710
MBT	10.1 (2.5)	0.1–1 920	34.4 (4.0)	0.2–260
TPT	17.1 (4.0)	0.2–2 330	21.3 (3.0)	0.4–260
DPT	2.57 (1.5)	0.1–166	2.0 (1.5)	0.5–14
MPT	7.04 (2.5)	0.1–198	11.7 (2.5)	0.1–86

DBT: dibutyltin; DPT: diphenyltin; MBT: monobutyltin; MPT: monophenyltin; TBT: tributyltin; TPT: triphenyltin

Sources: EC (2003); EFSA (2004)

DBT concentrations were below the detection limit (i.e. <1.0 ng/g [0.5 ng/g as Sn] wet weight) in all samples of fish (cod, haddock, perch and trout); concentrations ranged between 3.1 ng/g (1.6 ng/g as Sn) in fresh clams and canned cockles and 46.7 ng/g (23.9 ng/g as Sn) in canned mussels (Forsyth & Cléroux, 1991). Eight per cent of 1031 samples of turkey liver contained DBT (limit of detection 0.04 mg/kg as Sn), which resulted from the use of DBT dilaurate as a coccidiostat and anthelminthic in turkeys; DBT was not detected in companion muscle tissue samples (Epstein et al., 1991). DBT was the predominant butyltin present in Canadian wines, with 23.2% of samples tested containing 1.1–138.1 ng/mL (Forsyth, Weber & Cléroux, 1992).

Monobutyltin (MBT) concentrations were below the limit of detection of <1.0 ng/g (<0.7 ng/g as Sn) wet weight in all samples of fish (cod, haddock, perch and trout), but concentrations ranged between 1.2 ng/g (0.8 ng/g as Sn) in fresh clams and 5.9 ng/g (4.0 ng/g as Sn) in canned mussels (Forsyth & Cléroux, 1991). A limited number of fruit drinks contained MBT: 100–200 ng/L (70–140 ng/L as Sn) in four out of 42 samples, with a limit of detection of 60 ng/L (41 ng/L as Sn) (Forsyth & Cléroux, 1991).

Out of 15 samples of edible oils, five contained both dioctyl tin (DOT), at 25.2–113.3 ng/g (8.7–39.1 ng/g as Sn), and monooctyltin (MOT), at 5.5–26.3 ng/g (2.8–13.5 ng/g as Sn). A limited number of fruit drinks contained DOT in the range of 900–4300 ng/L (300–1500 ng/L as Sn) in three out of 42 samples and MOT in the range of 4500–16 300 ng/L (2300–8400 ng/L as Sn) in five out of 42 samples (DS Forsyth, Food Directorate, Health and Welfare Canada, personal communication, 1992). DOT was not detected in limnic or marine biota (Rüdel et al., 2001; Sternbeck, Fäldt & Österåset, 2006; Rantakokko et al., 2010).

The European Food Safety Authority (EFSA) concluded that, based on fully aggregated European data for fish and fishery products, the estimated mean concentrations of TBT, DBT and TPT are 7.0, 2.5 and 4.0 µg/kg fresh weight, respectively; the corresponding mean concentrations are about 4- to 7-fold higher (EFSA, 2004).

TeBT was not detected in samples of oysters, clams, Dungeness crab and mussels from Washington state in a screening-level study (Johnson, 2000). In Germany, concentrations in zebra mussels ranged from <1 to 4 µg/kg (round weight – weight of whole fish before processing) as Sn, and concentrations in brace muscle tissue ranged from <1 to 13 µg/kg (round weight) as Sn (Gies et al., 1978). TeBT was not detected in mussels collected in 2000 from three locations in the Adriatic Sea (Nemanič et al., 2002). TeBT concentrations measured in Pacific oysters collected off the coast of Taiwan in 2002 ranged from not detectable to a maximum of 29.5 ng/g wet weight as Sn (Hsia & Liu, 2003). In a multiyear national monitoring programme in the USA that measured TeBT in water, sediment and bivalve tissue collected in and around commercial harbours, shipyards/dry docks, marinas and ecologically significant areas, the range of geometric mean TeBT concentrations in bivalve tissues in 1993–2000 was not detectable to 18.4 ng/g dry weight as Sn (Parametrix 1994a,b, 1995, 1996, 1997, 1998, 1999, 2001). TeBT was detected in five of 67 various tissue samples from cobia collected off the coast of Taiwan in 2003 and 2004; the maximum concentration measured was 90 ng/g wet weight as Sn (Liu, Hsia & Huang, 2006).

2.4 Estimated total exposure and relative contribution of drinking-water

Based on fish and seafood consumption in Norway, EFSA (2004) estimated the combined TBT, DBT and TPT intake to be 0.018 µg/kg bw/day (approximately 1 µg/day for a 60 kg adult) from the median concentration data and 0.083 µg/kg bw/day from the mean concentration data.

In a Japanese market basket study, TBT was detected in seafood (5.2 µg/day in 1993), including fish, molluscs and crustaceans, and in vegetables (0.2 µg/day in 1993), excluding green vegetables and seaweed. TBT was not detected in rice, cereals, grains, potatoes, sugar, cakes, fats, oils, bean products, fruits, green vegetables, seasonal beverages, meats, eggs, milk, dairy products or cooked meats. TPT was detected only in seafood (0.4 µg/day in 1993), including fish, molluscs and crustaceans (Tsuda et al., 1995). Daily intakes of TBT and TPT in Shiga Prefecture, Japan, were estimated to be 6.9 µg and 5.4 µg in 1991, and 6.7 µg and 1.3 µg in 1992, respectively, from a separate market basket study. Daily intakes of TBT and TPT were estimated by the duplicate portion method to be 4.7 µg and 2.7 µg in 1991, and 0.7 µg and 0.7 µg in 1992, respectively (Tsuda et al., 1995).

It is difficult to assess human exposure to organotins via drinking-water, because the only available concentrations in drinking-water were measured in tap water from PVC pipes, with detection usually below a few hundred nanograms. However, most of the organotins, except for octyltin compounds, have been detected as contaminants in environmental waters, which include fresh waters that are possible drinking-water sources. The concentrations were mostly between the detection limits and hundreds of nanograms per litre. Based on most of the data given above, the daily intakes (assuming drinking-water consumption of 2 L/day) are likely to be very low – a few hundred nanograms per day at the most – which is less than the daily intake through food.

Organotins have also been detected in a variety of consumer products (e.g. diapers, PVC gloves, silicone-soaked baking paper), and use of these products could also lead to human exposure (IPCS, 2006). According to the European Disposables and Nonwovens Association (EDANA), the release sheet of a nappy or female hygiene product has been recorded in the past as a major source of organotins in EDANA products; following requests made to suppliers, the use of organotins in the production of these release sheets has since been phased out, and other catalysts are now used in their production (RPA, 2007).

3 Toxicokinetics and metabolism in animals and humans

3.1 Absorption

Limited studies have been undertaken on absorption. After ingestion, organotins may be converted in part to their chlorides, which are absorbed in the gastrointestinal tract (DFG, 2001).

The absorption of DOTC in orally treated rats was calculated to be approximately 20% of the dose, because approximately 80% of the ^{14}C-labelled DOTC radioactivity was excreted in the faeces during the first day after administration (Penninks, Hilgers & Seinen, 1987). Rats that were administered a single oral dose of monoethyltin trichloride (12 mg/kg bw as Sn) excreted 92% of the dose in faeces and 1.2% in urine, suggesting that at least 8% of the dose was absorbed (Bridges, Davies & Williams, 1967). In rats dosed orally with monooctyltin trichloride (MOTC) at 25 mg/kg bw, estimated absorption was 0.03% of the dose (IPCS, 2006).

The absorption of TBTO in rats was 20–55%, depending on the vehicle (EFSA, 2004). Following administration of a single oral dose (10 mg/kg bw) of ^{14}C-labelled triphenyltin hydroxide (TPTOH) to rats, 40% of the dose was absorbed (Kellner & Eckert, 1986). When ^{113}Sn-radiolabelled TPTOH (2 mg/kg bw) was orally administered to rats, absorption was calculated to be 12–28% within 30 hours (Kellner, Eckert & Buerkle, 1989).

3.2 Distribution

Organotins have both lipophilic and ionic properties. Whereas the former may favour their accumulation in lipids, the latter enable organotins to bind to proteins and glutathione (EFSA, 2004). Organotins tend to be primarily distributed in the liver and kidney following oral administration to rodents (Evans, Cardarelli & Smith, 1979; Mushak, Krigman & Mailman, 1982; EFSA, 2004). Butyltins were detected in liver samples from men and women in Poland, Denmark, Germany and Japan. The total butyltin burden was in the range 1.1–96 µg/kg wet weight. DBT appears to be the main butyltin compound deposited in human liver (EFSA, 2004).

The United States National Toxicology Program reported organotin and total Sn blood levels in Danish women of reproductive age (US NTP, 2016). The frequency of detection was 0% for monophenyltin (MPT), TPT, DPT and TBT; 2.1% for DBT; and 10.6% for MBT. Based on total Sn analysis of 47 serum samples, total Sn was detected in 100% of samples; the median was 1.51 ng/mL and the average was 1.86 ng/mL. In whole blood, the median was 1.70 ng/mL and the average was 1.79 ng/mL (n = 10).

TBTO may cross the placenta to some extent, as shown by the presence of the radiolabel in rat fetuses after administration of a single oral dose (25 mg/kg bw) of ^{113}Sn-labelled TBTO to the mother (Hümpel et al., 1986). After administration of a single oral dose (22 mg/kg bw) of dibutyltin diacetate (DBTA) to pregnant rats on gestation day (GD) 8, both DBT and MBT were detected in the embryos, indicating placental transfer (Noda, Morita & Baba, 1994). Nakamura et al. (1993) also detected DBT in embryos of pregnant rats dosed orally on GDs 7–17.

Pregnant Sprague–Dawley rats were exposed to 0, 10 or 25 ppm dibutyltin dichloride (DBTC) in drinking-water from GD 6 to postnatal day (PND) 21 (Moser, McGee & Ehman, 2009). Beginning on PND 3, half the litters were directly dosed every 2–3 days via gavage with 0, 1 or 2.5 mg/kg DBTC at doses matching the water concentration. For Sn analysis, brain and blood samples were collected from culled pups at PND 2, from pups and dams at PND 21, and from adult offspring at PND 93. At all ages, brain Sn levels were higher than blood levels. At culling, in the directly dosed pups at weaning, and in dams at weaning, Sn levels in both tissues were linearly related to dose. Weanling pups without direct dosing had lower levels than culled pups or dams, indicating that lactational exposure was minimal even during maternal exposure. In the adult offspring at PND 93, Sn levels persisted in brains of directly dosed rats, and the high-dose females had higher levels than high-dose males. No Sn was detected in adult blood.

3.3 Metabolism

Organotins can hydrolyse in aqueous media. For instance, TPT compounds containing an anionic group such as chloride (triphenyltin chloride – TPTC) or acetate (triphenyltin acetate – TPTA) can hydrolyse at ambient temperatures in the pH range of 3–8 to the hydroxide (TPTOH) (Buerkle, 1985). Accordingly, hydrolysis of organotins can occur in the stomach.

In vitro, TBT was metabolized to DBT, hydroxybutyltins, butanol and butene (Kimmel, Fish & Casida, 1977), whereas diethyltin, triethyltin (TET) and tetraethyltin appeared to form ethene

and ethane (Wiebkin, Prough & Bridges, 1982). Radiolabelled carbon dioxide and butene were detected as exhaled metabolites of [^{14}C]-DBT diethanoate and [^{14}C]-TBT ethanoate after gavage dosing in mice (Kimmel, Fish & Casida, 1977). Radiolabelled TPT derivatives comprised about 57% of extracts from faeces and urine after gavage dosing of ^{113}Sn-labelled TPTA in mice, and half of the extracts were metabolized to dephenylated or polar unknown metabolites (Kimmel, Fish & Casida, 1977). In addition to the metabolites generated by mixed-function oxidases, mercapturic acid derivatives were found in the urine of rats injected intraperitoneally with tributyltin chloride (TBTC) at 4.5 mg/kg bw (Suzuki et al., 1999). Despite extensive metabolism in the liver, a first-pass effect does not seem to reduce the systemic availability to any great extent (Hümpel et al., 1986).

Following administration of ^{14}C-labelled dibutyltin diacetate to mice, the faeces contained a large amount of non-metabolized compound (41% of the dose) and some MBT (3.5% of the dose). The formation of MBT from DBT may involve both non-enzymatic dealkylation and cytochrome P450–dependent hydroxylation reactions (Kimmel, Fish & Casida, 1977).

TPT has been shown in in vivo studies with rats to undergo extensive metabolism to form dearylated metabolites, which included DPT and MPT as well as a significant portion of non-extractable bound residues (the sulfate conjugates of hydroquinone, catechol and phenol). In faeces, the major substance present was unchanged parent compound (Fish, Kimmel & Casida, 1976; Kimmel, Fish & Casida, 1977; Buerkle et al., 1986). TPT was dearylated in microsomal systems in low amounts when dithiothreitol was added (Ohhira, Watanabe & Matsui, 2003, 2004). After administration of a single oral dose of tetraphenyltin (TePT) to male Wistar rats, the highest concentrations of DPT were observed in the liver and kidney (Ohhira, Watanabe & Matsui, 2003).

Hydroxylation and dealkylation in vivo of octyltin compounds will be less than that of the butyltins, because the extent of in vitro microsomal metabolism of various tri-*n*-alkyltins decreases with increasing chain length (EFSA, 2004). Monooctyltin is the major metabolite of dioctyltin in the liver, kidney and brain of rats (Kishi et al., 2006).

After intraperitoneal injection of dimethyltin dichloride (DMTC) in both mice and rats over 4 consecutive days, high concentrations of dimethyltin (DMT) and a time-dependent increase in trimethyltin (TMT) concentrations during treatment were observed, with the concentrations gradually decreasing after treatment ceased (Furuhashi et al., 2008).

Human liver microsomes can metabolize TBT and TPT to dephenylated metabolites in small amounts (Ohhira, Watanabe & Matsui, 2003).

3.4 Elimination

After oral administration, it appears that the principal route of excretion of organotins is via the faeces (Evans, Cardarelli & Smith, 1979). Bile is also a significant route for some compounds, such as tetraalkyltins (Iwai et al., 1982).

After a week of feeding rats DBTC at 100 mg/kg diet, DBT elimination from kidney, liver, spleen and thymus was rapid, with DBTC half-lives of several days in each organ (Arakawa, Wada & Manabe, 1983).

Eighty per cent of a single oral dose of DOTC (2 mg/kg bw) in rats was excreted in the faeces within 2 days. After 3 days, the excretion of radioactivity followed first-order kinetics, with a half-life of 8.9 days. After intravenous administration, 66% of the radioactivity was excreted

in the faeces, with a half-life of 8.3 days. The percentages of radioactivity excreted in the urine were 11% and 22% following intravenous and oral dosing, respectively. The urinary excretion of ^{14}C-labelled DOTC appeared to be independent of the body burden, because the daily urinary excretion of radioactivity was nearly constant during the 25-day experimental period after both oral and intravenous administration (Penninks, Hilgers & Seinen, 1987).

4 Effects on humans

Several case reports associate acute inhalation, dermal or oral exposure to TBT, TPT or TMT with various health effects (EFSA, 2004). TET intoxication in humans has been reported to be associated with seizures, visual disturbances and paraparesis. However, causality cannot be established, and none of the reports contains sufficient information to characterize the exposure or any dose–response relationships. No information was found regarding the toxicity of organotin compounds following long-term human exposure.

Ross et al. (1981) studied 22 male chemical workers exposed to trimethyltin chloride during 1978 in a plant in the USA following a spillage (inhalation and dermal exposure presumed). The high-exposure group showed a significantly higher incidence of nonspecific symptoms, such as forgetfulness, fatigue, weakness and loss of motivation, and specific symptoms, such as bouts of depression and attacks of rage; some symptoms persisted for at least 3 years.

Human data summarized by Boyer (1989) suggest that TBTO is a potent dermal non-allergic irritant. Several case reports claim irritation of the respiratory tract following acute inhalation exposure to TBTO (Knobeloch & Anderson, 1991; Shelton, Urch & Tario, 1992; Wax & Dockstader, 1995).

Two cases of inhalation poisoning by TPTA reported dizziness, nausea, photophobia, general malaise, weakness and dryness of the mouth that disappeared within days (Manzo et al., 1981). In other reports on severe intoxications with TPT, various neurotoxic symptoms were described, including a cerebellar syndrome, hearing impairment and loss of consciousness with paroxysmal activity on electroencephalography (Wu, Chang & Chiu, 1990; Lin et al., 1998). A survey of hypersensitivity reactions to a series of 36 TPT-containing pesticide formulations among 652 subjects in Italy showed that TPT is a moderately strong irritant, but not an allergen (Lisi, Carraffini & Assalve, 1987). Three male patients developed acute nephropathy following ingestion of TPTA, which appeared to result mainly from proximal renal tubular damage with a benign and reversible course (Lin & Hsueh, 1993).

5 Effects on experimental animals and in vitro test systems

5.1 Acute exposure

5.1.1 Tetrasubstituted compounds

The oral median lethal dose (LD_{50}) of TeBT for rats was >2000 mg/kg bw (Mullaney, 2004). The oral LD_{50} of TeOT for rats was >2000 mg/kg bw (Prinsen, 2003).

5.1.2 Trisubstituted compounds

The oral LD_{50} for TMT was 14.7 mg/kg bw in rats and ranged from 3.16 to 4.64 mg/kg bw in mice (Tang et al., 2013). The oral LD_{50} values for TBT ranged from 94 to 234 mg/kg bw in rats and from 44 to 230 mg/kg bw in mice (IPCS, 1990). The oral LD_{50} values for TPT (TPTA

and TPTOH) ranged from 140 to 298 mg/kg bw in rats and from 81 to 93 mg/kg bw in mice (EC, 1997). The oral LD_{50} for TBTC was 122 mg/kg bw (OECD, 2010).

5.1.3 Disubstituted compounds

The oral LD_{50} values for DMT in rats ranged from 73.9 to 383.0 mg/kg bw (AME, 1971; Klimmer, 1971; Figge & Koch, 1973; Cannon Laboratories, 1979; Tang et al., 2013), and the LD_{50} for DMT in mice was 316.0 mg/kg bw for males and 215.0 mg/kg bw for females (Tang et al., 2013). In rats, the oral LD_{50} values were 58–219 mg/kg bw for DBTC (Klimmer & Nebel, 1960; Schering AG, 1969a; Klimmer, 1971) and 172–520 mg/kg bw for dibutyltin oxide (DBTO) (M&T Chemicals, Inc., 1978; Ciba-Geigy Ltd, 1983a). In mice, the oral LD_{50} was 25 mg/kg bw and 24 mg/kg bw for DBTC and DBTO, respectively (IPCS, 1980). The acute oral LD_{50} values for dioctyltins in rodents ranged from 880 to 8500 mg/kg bw (Klimmer, 1969; Pelikan, Cerny & Polster, 1970; Ciba-Geigy Ltd, 1982a). The oral LD_{50} for DOTC in rats was more than 4000 mg/kg bw (Schering AG, 1968).

The intraperitoneal LD_{50} for DMT was 31.6 and 46.4 mg/kg bw for male and female rats, respectively, and 68.1 and 59.9 mg/kg bw for male and female mice, respectively (Tang et al., 2013).

5.1.4 Monosubstituted compounds

The oral LD_{50} values for monomethyltin (MMT) in rats ranged from 566 to 3300 mg/kg bw (Hill-Top Toxicology, 1978; Cannon Laboratories, 1979; Mesch & Kugele, 1992; Walterson, Sangfors & Landner, 1993). The oral LD_{50} values for MBT in rats ranged from 357 to 3200 mg/kg bw (Schering AG, 1969b; NIOSH, 1976; Atochem NA, 1991a; Mesch & Kugele, 1992; Walterson, Sangfors & Landner, 1993). The oral LD_{50} for monobutyltin trichloride (MBTC) in mice was 1400 mg/kg bw (Pelikan & Cerny, 1970). The oral LD_{50} values for MOT in rats ranged from 2200 to 3800 mg/kg bw (Schering AG, 1971; Ciba-Geigy Ltd, 1982b; Hess & Schweinfurt, 1989; Witco, 1992).

5.2 Short-term exposure

5.2.1 Tetrasubstituted compounds

The repeated-dose toxicity of TeBT (96.52% purity) was evaluated in a combined repeated-dose and reproduction/developmental toxicity screening test (OECD TG 422) conducted in rats at doses of 0, 100, 300 or 2000 mg/kg diet. At 300 mg/kg diet (equivalent to 16–24 mg/kg bw/day), decreased spleen weight and thymic lymphoid depletion were observed. At 2000 mg/kg diet (100–130 mg/kg bw/day), the following effects were observed: decreased body weights and food consumption; decreased spleen weights in males and decreased thymus weights in both sexes; increased thrombocytes and decreased prothrombin time; increased gamma-glutamyl transferase, cholesterol and phospholipids; blood in the lymph nodes; and thymic lymphoid depletion. The no-observed-adverse-effect level (NOAEL) for subchronic toxicity was 100 mg/kg diet (equivalent to 5–8 mg/kg bw/day for both sexes), and the lowest-observed-adverse-effect level (LOAEL) was 300 mg/kg diet (Waalkens-Berendsen, 2004a).

The repeated-dose toxicity of TeOT (90.8% purity) in rats was evaluated in a combined repeated-dose and reproductive/developmental toxicity screening test (OECD TG 422) conducted in rats at doses of 0, 500, 1500 or 7500 mg/kg bw/day in diet. Based on the observed effects in the 7500 mg/kg diet group (decreased thymus weight, thymic lymphoid depletion

and macrophage accumulation), the NOAEL for subchronic toxicity was 1500 mg/kg diet (equivalent to 86–99 mg/kg bw/day for males and 80–141 mg/kg bw/day for females), and the LOAEL was 7500 mg/kg diet (445–480 mg/kg bw/day for males and 426–624 mg/kg bw/day for females) (Waalkens-Berendsen, 2004b).

The repeated-dose toxicity of TePT (97.9% purity) was evaluated in a combined repeated-dose and reproductive/developmental toxicity screening test (OECD TG 422) conducted in rats at doses of 0, 4, 20, 100 or 500 mg/kg bw/day. No adverse effects were observed at any dose, and the NOAEL for subchronic toxicity was 500 mg/kg bw/day (the highest dose) (MHLW, 2008).

5.2.2 Trisubstituted compounds

In rats fed TBTO at 0, 5, 20, 80 or 320 mg/kg diet (0, 0.25, 1.0, 4.0 or 16.0 mg/kg bw/day) for 4 weeks, increases in alanine aminotransferase, aspartate aminotransferase and immunoglobulin M (IgM), and decreases in white blood cell counts (mainly lymphocytes), serum glucose, liver glycogen, haemoglobin/haematocrit and thymus weight were seen at and above 1.0 mg/kg bw/day. Splenic iron stores were depleted, and sinus erythrocytosis in the mesenteric lymph nodes was seen at all doses (Krajnc et al., 1984). In a 1-month feeding study in rats given TBTO at 0, 5 or 25 mg/kg diet (0, 0.8 or 2.9 mg/kg bw/day), haemorrhage in the lymph nodes was observed at 5 mg/kg diet and higher, with a LOAEL of 0.8 mg/kg bw/day (Bressa et al., 1991). In a 6-week feeding study in rats given TBTO at 0, 20 or 80 mg/kg diet (0, 1 or 4 mg/kg bw/day), decreased serum insulin, decreased thyroid activity (as assessed by thyroid stimulating hormone and thyroxine levels), and corresponding histological changes in the pituitary and thyroid were observed at the highest dose (4 mg/kg bw/day) (Krajnc et al., 1984).

In a 1-month feeding study in rats given TBTC at 0, 5 or 25 mg/kg diet (0, 0.4 or 1.7 mg/kg bw/day), haemorrhage in the lymph nodes was observed at 5 mg/kg diet and higher, with a LOAEL of 0.4 mg/kg bw/day (Bressa et al., 1991).

In a 14-day repeated-dose dietary study of TBTC in male rats, doses of 50 and 150 mg/kg (equivalent to about 2.5 and 7.5 mg/kg bw/day) resulted in decreased thymic cell counts, decreased thymus weights, iron in the spleen and increased liver weights. Reduced body and brain weights, and reduced food consumption were also seen at the highest dose only (Snoeij et al., 1985). A NOAEL was not determined; the LOAEL was established at 15 mg/kg diet (equivalent to 0.75 mg/kg bw/day), based on decreased spleen weights and reddening in lymph nodes.

When cynomolgus monkeys were given a daily (6 days/week) oral TBTO dose of 0 or 0.160 mg/kg bw for 22 weeks, the total leukocyte count was lower in treated monkeys during weeks 8–10 and 16–20 than in controls (Karrer et al., 1992).

In a 3-month study in mice fed TPTOH at 0, 4, 20 or 100 mg/kg diet, a NOAEL of 20 mg/kg diet (3.44–4.12 mg/kg bw/day) was identified, based on changes in haematological and biochemical parameters (e.g. reduction in erythrocyte count and haemoglobin level; increase in platelet count; decrease in immunoglobulin G [IgG], immunoglobulin A and IgM [females only]) at 100 mg/kg diet (Suter & Horst, 1986a). In a 13-week study in rats fed TPTOH at 0, 4, 20 or 100 mg/kg diet, the levels of some serum enzymes (alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase) were increased at 100 mg/kg diet. In females, white blood cells were decreased in the middle and high-dose groups. The effects seen at 20 mg/kg diet were not considered to be of toxicological relevance by the European

Commission Coordination Group (EFSA, 2004). A NOAEL of 20 mg/kg diet (equal to 1.56–1.72 mg/kg bw) was identified (Suter & Horst, 1986b).

In a 1-year study in which dogs were fed TPTOH at 0, 2, 6 or 18 mg/kg diet, the NOAEL was 18 mg/kg diet (0.593 mg/kg bw/day); no effects on haematological or biochemical parameters were observed at the highest dose tested (Sachose et al., 1987).

5.2.3 Disubstituted compounds

In a 2-week study in rats fed DBTC at 0, 50 or 150 mg/kg diet (0, 2.5 or 7.5 mg/kg bw/day), reduced thymus weight was observed at both treatment doses (Penninks & Seinen, 1982). When DBTC was fed to rats at 0, 10, 20, 40 or 80 mg/kg diet (0, 0.5, 1, 2 or 4 mg/kg bw/day) for 90 days, reduction in feed intake, depressed growth and mild anaemia were noted at the highest dose; thus the NOAEL was 2 mg/kg bw/day, although effects on the thymus were not investigated (Gaunt et al., 1968).

In a 2-week study in rats fed DOTC at 0, 50 or 150 mg/kg diet (0, 2.5 or 7.5 mg/kg bw/day), the LOAEL was 2.5 mg/kg bw/day, based on decreased relative thymus and spleen weights (Penninks & Seinen, 1982). In a 6-week rat study using the same dosing regimen, the principal effect was a reduction in thymus weight at both doses (Seinen & Willems, 1976). A weekly oral DOTC dose of 500 mg/kg bw for 8 weeks reduced thymus weight and induced immunodeficiency in mice, whereas a dose of 100 mg/kg bw did not cause such effects (Miller, Maisey & Nicklin, 1986). A reduction in both thymus weight and immunocompetence was observed in rats fed diets containing DOTC at 75 mg/kg (about 3.8 mg/kg bw/day) for 8 or 12 weeks (Miller & Scott, 1985).

5.2.4 Mixtures of disubstituted and monosubstituted compounds

In a 90-day drinking-water study, rats were administered a mixture of DMTC and MMTC (90%:10%) at concentrations of 0, 25, 75 or 200 mg/L (0, 1.6, 5.2 or 15.5 mg/kg bw/day for males and 0, 2.2, 6.7 or 19.4 mg/kg bw/day for females) (ClinTrials BioResearch Ltd**,** 1997). Another 90-day dietary study in rats used a different mixture of DMTC and MMTC (63.5%:33.5%) at dietary concentrations of 0, 1, 6, 15 or 200 mg/kg (0, 0.06, 0.39, 0.98 or 16.8 mg/kg bw/day for males and 0, 0.07, 0.41, 1.02 or 17.3 mg/kg bw/day for females) (TNO, 1999). In both studies, the critical end-point was neurotoxicity: tremors and convulsions were observed in a dose-related manner. Histopathology (feed study) confirmed neuronal death in the cerebellum and brain lesions. The NOAEL was 0.98 mg/kg bw/day in the feeding study, and the LOAEL was 1.6–2.2 mg/kg bw/day in the drinking-water study.

In a 90-day repeated-dose study of a mixture of MMTC and DMTC (82.85%:9.29%) in rats fed at 0, 30, 150 or 750 mg/kg diet (MMTC doses of 0, 1.9, 9.8 or 49.7 mg/kg bw/day for males and 0, 2.1, 10.2 or 53.6 mg/kg bw/day for females), the NOAEL was 150 mg/kg diet (about 10 mg/kg bw/day), based on changes in haematology, clinical chemistry, urine analysis, organ weights and neurobehavioural parameters, and an increased incidence of lesions of the hippocampus (Appel & Waalkens-Berendsen, 2004a). In a second 90-day study, rats were administered MMTC and DMTC (78%:22%) at 0, 20, 100 or 500 mg/kg diet (0, 1.0, 5 or 26 mg/kg bw/day for males and 0, 3.6, 16 or 73 mg/kg bw/day for females). A definitive NOAEL could not be determined, as the LOAEL was 20 mg/kg diet, based on slightly increased relative kidney weight in females and slight epithelial hyperplasia in the bladder of two out of nine females (TNO, 1978). The most significant contributor to the different toxicities

in these two studies is likely to be the mono/di ratio of the test material. Both studies reported similar organ weight changes, particularly in the kidneys and thymus (OECD, 2008a).

In a 90-day repeated-dose feeding study of an MBTC and DBTC mixture (99.72%:0.21%), rats were administered the test substance at 0, 300, 1500 or 7500 mg/kg diet. The NOAEL for MBTC was 1500 mg/kg diet (96 mg/kg bw/day for males and 101 mg/kg bw/day for females), based on changes in haematology, clinical chemistry and liver weights at 7500 mg/kg diet (Appel & Waalkens-Berendsen, 2004b).

A 90-day repeated-dose dietary feeding study in rats administered a mixture of DOTC and MOTC (94.09%:2.25%) at 0, 10, 100 or 300 mg/kg diet (DOTC dose of 0, 0.7, 7 or 19–20 mg/kg bw/day). This identified a LOAEL of 10 mg/kg diet (0.7 mg/kg bw/day), based on decreased monocytes and thymus weights in females (Appel & Waalkens-Berendsen, 2004c).

In a 90-day repeated-dose feeding study in rats administered a MOTC and DOTC mixture (85.50%:11.07%) at 0, 10, 100 or 500 mg/kg diet (MOTC dose of 0, 0.6, 6.4 or 31.5 mg/kg bw/day for males and 0, 0.7, 6.8 or 32.9 mg/kg bw/day for females), the NOAEL for MOTC was 6.4 mg/kg bw/day, based on increased alkaline phosphatase, decreased liver and thymus weights, and slight to severe thymic lymphoid depletion at 31.5 mg/kg bw/day (Appel & Waalkens-Berendsen, 2004d). A second 90-day repeated-dose dietary feeding study of MOTC and DOTC (94%:6%) in weanling rats, which was not conducted in compliance with good laboratory practice, used dietary MOTC concentrations of 0, 30, 100, 300 and 1000 mg/kg diet (0, 1.5, 5, 15 and 50 mg/kg bw/day). The LOAEL was 1.5 mg/kg bw/day, based on decreased thymus weights in females at the lowest dose tested (Rohm & Haas, 1976). The mixture proportions in the four short-term studies described above are shown in Table 5.1.

Table 5.1. Mixtures of organotins used in short-term exposure studies

1) Monomethyltin trichloride (purity of total alkyltins: 88%)[a]		2) Monobutyltin trichloride (purity of total alkyltins: 99.72%)[a]		3) Dioctyltin dichloride (purity of total alkyltins: 92.1%)[a]		4) Monooctyltin trichloride (purity of total alkyltins: 89.2%)[a]	
Alkyl group distribution (%; mass/mass)							
Monomethyltin trichloride	82.85	**Monobutyltin trichloride**	99.72	**Dioctyltin dichloride**	94.09	Monooctyltin trichloride	85.50
Dimethyltin dichloride	9.29	Dibutyltin dichloride	0.21	Monooctyltin trichloride	2.25	Dioctyltin dichloride	11.07
Trimethyltin chloride	0.02	Tin tetrachloride	0.06	Trioctyltin chloride	0.70	Trioctyltin chloride	0.50
Tin tetrachloride	4.68			Tin tetrachloride	0.05	Tin tetrachloride	0.03
Me2ClSnCH2SnCl3	0.59			Mono-i-butyltin trichloride	0.01	Mono-i-butyltin trichloride	0.42
MeCl2SnCH2SnCl3	1.78			Octyl-i-butyltin dichloride	0.78	Monobutyltin trichloride	0.03
Cl3SnCH2SnCl3	0.80			Octylbutyltin dichloride	0.16	Monooctyltin trichloride isomers	0.91
				Octylhexyltin dichloride	0.03	Octyl-i-butyltin dichloride	0.12
				Dioctyltin dichloride isomers	0.64	Octylbutyltin dichloride	0.05
				Octyldodecyltin dichloride	0.03	Monododecyltin trichloride	0.03
				Monohexadecyltin trichloride	0.03	Dioctyltin dichloride isomer	0.06
				Octylhexadecyltin dichloride	1.19	Monohexadecyltin trichloride	1.10
				Tetraoctyltin	0.04	Octylhexadecyltin dichloride	0.17

[a] Refers to the proportion of the mixture that consists of organotin compounds. Identities and percentages of non-organotin impurities are not shown in this table.

Sources: 1) Appel & Waalkens-Berendsen (2004a); 2) Appel & Waalkens-Berendsen (2004b); 3) Appel & Waalkens-Berendsen (2004c); 4) Appel & Waalkens-Berendsen (2004d)

5.3 Long-term exposure and carcinogenicity

5.3.1 Trisubstituted compounds

In mice fed TBTO at 0, 5, 25 or 50 mg/kg diet (0, 0.75, 3.75 or 7.5 mg/kg bw/day) for 18 months, survival was reduced in all treated animals, but tumour incidences were not increased (Daly, 1992).

In an 80-week study, mice received dietary TPTOH at 0, 5, 20 or 80 mg/kg diet. Body weight was decreased in females in the 20 and 80 mg/kg diet groups, and in males in the 80 mg/kg diet group. A decrease in IgM concentrations was seen at all doses. The incidence of hepatocellular adenomas in both sexes and the incidence of hepatocellular carcinomas in females were increased at the highest dose (21.76 mg/kg bw/day). The NOAEL was 5 mg/kg diet (1 mg/kg bw/day), based on decreased body weight gain in females (Tennekes et al., 1989a). Data on

serum IgM were not used to derive the NOAEL, because the method of analysis has not been evaluated in rodents (WHO, 1992).

In a 2-year chronic toxicity and carcinogenicity study, rats were fed TBTO at 0, 0.5, 5 or 50 mg/kg diet (0, 0.025, 0.25 or 2.5 mg/kg bw/day). At the high dose, mortality was increased near the end of the study, body weight was reduced, and there were variable and sometimes transient effects on various parameters (endocrine system, haematology, immunoglobulin levels). Increased incidences of benign pituitary tumours were observed in both sexes at the low and high doses, whereas other endocrine-related tumours (phaeochromocytomas in the adrenal medulla and parathyroid adenomas) were found at the high dose only. There were marginal effects (increases in thrombocytes and IgM levels) at a dose of 5 mg/kg diet. The NOAEL was 0.5 mg/kg diet (0.025 mg/kg bw/day), based on changes in haematological and immunological parameters (Wester et al., 1988, 1990).

In a 2-year study in rats administered TPTOH at 0, 0.5, 1, 2, 5 or 10 mg/kg diet (0, 0.025, 0.05, 0.1, 0.25 or 0.5 mg/kg bw/day), slight changes in the immune system, such as spleen weight reduction, decreased white blood cell counts and reduction in thymus weight, were observed, but there was no increased incidence of tumours. A NOAEL of 2 mg/kg diet (0.1 mg/kg bw/day) was identified, based on effects on the immune system (Til, Feron & de Groot, 1970). In another 2-year feeding study conducted in rats with TPTOH at 0, 5, 20 or 80 mg/kg diet (0, 0.4, 1.6 or 3.2 mg/kg bw/day), dose-related mortality was seen in females. A decrease in IgG concentrations was reported in all dosed groups, and IgM was increased at the two highest doses. Increases in the incidence of pituitary adenoma in females in the 20 and 80 mg/kg diet groups, and in Leydig cell tumours in males in the highest-dose group were accompanied by associated non-neoplastic lesions (such as hyperplasia). A NOAEL could not be established because of the increased mortality in females and reduced serum immunoglobulin levels at the lowest dose (Tennekes et al., 1989b). It was concluded that the tumour incidences did not indicate a genotoxic hazard for humans, as a result of the limited evidence of genotoxic potential (WHO, 1992).

5.3.2 Disubstituted compounds

In a 78-week study, F344 rats were fed diets containing DBT diethanoate at 0, 66.5 or 133 mg/kg (0, 3.33 and 6.65 mg/kg bw/day), and B6C3F1 mice were fed diets containing the same organotin at 0, 76 or 152 mg/kg (0, 9.9 or 19.8 mg/kg bw/day). Nonsignificant increased incidences of hepatocellular adenomas in female mice, and both hepatocellular adenomas and carcinomas in male mice were noted (NCI, 1979).

5.3.3 Mixtures of disubstituted and monosubstituted compounds

In a 2-year dietary study in rats, a 2:1 mixture (66%:33%) of MOTC and DOTC administered at 0, 5, 15, 50 or 150 mg/kg diet (0, 0.24, 0.69, 2.2 or 5.5 mg/kg bw/day for males and 0, 0.26, 0.74, 2.3 or 6.0 mg/kg bw/day for females) resulted in a significant increase in the incidence of primary tumours of the thymus (particularly thymic lymphomas). Incidences of malignant lymphoma were slightly but significantly increased at 50 mg/kg diet (4/60 males), 150 mg/kg diet (4/60 males) and 150 mg/kg diet (4/60 females). For females in the 150 mg/kg diet group, the incidences of primary tumours of the thymus (13/60) and thymic lymphoma (11/55) were also increased. Haematological changes were limited to an increased number of white blood cells in females in the 50 and 150 mg/kg diet groups at week 105. Thymic weights were increased in males in the 50 and 150 mg/kg diet groups, and in females in the 150 mg/kg diet group (Ciba-Geigy Ltd, 1986).

Brief summaries of unpublished long-term studies are available for other organotin mixtures. Almost all studies showed no carcinogenicity for mixtures of MMT and DMT in rats, and MOT and DOT in rats or dogs (Summer, Klein & Griem, 2003).

5.4 Genotoxicity

5.4.1 Tetrasubstituted compounds

TeBT was negative in all tests for genotoxicity conducted with or without metabolic activation, including standard and modified Ames assays using single and multiple strains of *Salmonella* Typhimurium and/or *Escherichia coli*, an SOS chromotest and a rec assay. TeBT was not clastogenic in an in vivo mouse micronucleus test (OECD, 2009e).

TeOT was negative in a standard in vitro Ames assay using multiple strains of *Salmonella* Typhimurium and *E. coli*, conducted with or without metabolic activation. TeOT was also negative in a standard in vivo mouse micronucleus test (OECD, 2009f).

TePT was negative in a standard in vitro Ames assay using multiple strains of *Salmonella* Typhimurium and *E. coli*, conducted with or without metabolic activation. It was positive with and without metabolic activation in an in vitro mammalian chromosomal aberration test (MHLW, 2008).

5.4.2 Trisubstituted compounds

Trimethyltin chloride induced aneuploidy in human peripheral lymphocytes in vitro (Jensen, Andersen & Ronne, 1991).

TBTO lacks in vitro and in vivo mutagenic potential (Davis et al., 1987; Yamada & Sasaki, 1993).

TBTC was negative in a standard in vitro Ames assay conducted with or without metabolic activation (Krul, 2003a), and in an SOS chromotest conducted without metabolic activation (Hamasaki et al., 1992). TBTC was positive in a preincubation assay using only strain TA100 without metabolic activation (Hamasaki et al., 1993) and in a rec assay conducted without metabolic activation (Hamasaki et al., 1992). In a micronucleus assay, TBTC was associated with a statistically significant but nonbiologically relevant increase in micronuclei, which suggests that TBTC is nonclastogenic in vivo (de Vogel, 2003a).

Triphenyltin oxide (TPTO) was not genotoxic in in vitro studies for gene mutations (Richold, Jones & Fleming, 1981; Milone & Hirsch, 1985a; Jung & Weigand, 1986), gene conversion (Milone & Hirsch, 1985b) or unscheduled DNA synthesis (Cifone & Myhr, 1985). TPTO is a weak in vitro clastogenic agent in the mouse lymphoma TK assay (DenBoer & Hoorn, 1985) and induced chromosomal aberrations in cultured human lymphocytes (Kirkland, 1985; Nunziata & Consonni, 1988). TPTC induced aneuploidy in human peripheral lymphocytes in vitro (Jensen, Andersen & Ronne, 1991). Its capacity to induce chromosomal aberrations has not been clearly shown in vivo (Chao et al., 1999).

5.4.3 Disubstituted compounds

DMTC was not mutagenic in Ames assays, a hypoxanthine–guanine phosphoribosyltransferase (HGPRT) assay or an SOS chromotest conducted with or without metabolic activation (Morton International, Inc., 1990a,b,c; Hamasaki et al., 1992) or in human peripheral lymphocytes in

vitro (Jensen et al., 1991). It was positive (with activation) and negative (without activation) in an assay for chromosomal aberrations (Morton International, Inc., 1990d), positive in a modified bacterial reverse mutation assay with *Salmonella* Typhimurium strain TA100 without activation and positive in a rec assay without activation (Hamasaki et al., 1992, 1993). DMTC was negative in an in vivo mouse micronucleus assay and an unscheduled DNA synthesis bioassay (Morton International, Inc., 1991; SRI International, 1993).

DBTC and DBTO were negative in standard Ames assays (Schering AG, 1979a; Krul, 2002a). Studies with DBT in yeast were also negative (Summer, Klein & Griem, 2003). DBTC was negative in HGPRT assays with fetal Chinese hamster lung cells (Schering AG, 1989a) and human peripheral lymphocytes (Jensen et al., 1991). In contrast, DBTC was positive in an HGPRT assay using Chinese hamster ovary cells (Li, Dahl & Hill, 1982), a modified Ames test (Hamasaki et al., 1993), a chromosomal aberration test (Schering AG, 1990), an SOS chromotest and a rec assay (Hamasaki et al., 1992; Sato et al., 1992). These results indicate that DBT compounds are potentially clastogenic in vitro. DBTC yielded both positive and negative results in in vivo mouse micronucleus assays (Atochem NA, 1991b; Schering AG, 1991).

DOTC was negative in the Ames test, in tests for the induction of unscheduled DNA synthesis and in an HGPRT assay (Schering AG, 1978, 1989b,c; Westendorf, Marquardt & Marquardt, 1986). It was not considered genotoxic based on a weight-of-evidence evaluation of a large battery of in vitro and in vivo assays (EC, 1999). Summer, Klein & Griem (2003) reviewed studies on octyltins using yeast cells; with the exception of a single study on DOTC at the highest concentration tested (10 mg/mL), all were negative. DOTC and dioctyltin oxide were negative in micronucleus assays (Krul, 2003b; de Vogel, 2004), and DOTC was negative in a sister chromatid exchange test (Ciba-Geigy, 1983b) and a covalent DNA binding assay (Ciba-Geigy, 1988a) conducted in vivo.

Diphenyltin dichloride induced aneuploidy in human peripheral lymphocytes in vitro (Jensen et al., 1991).

5.4.4 Monosubstituted compounds

MMTC was not mutagenic in standard Ames assays conducted with or without metabolic activation, and also yielded negative results in an SOS chromotest and a rec assay (Hamasaki et al., 1992, 1993; Krul, 2002b). MMTC was weakly positive in in vivo micronucleus assays (de Vogel, 2003b). Other in vivo tests (unscheduled DNA synthesis, host-mediated assay/mouse lymphoma cells, sister chromatid exchange and covalent DNA binding assays) were negative (reviewed in Summer, Klein & Griem, 2003).

MBTC yielded negative results in a standard Ames test (Krul, 2002c), a chromosomal aberration test (Ciba-Geigy, 1988b), a mammalian cell gene mutation assay (Ciba-Geigy, 1988c) and a rec assay (Hamasaki et al., 1992). MBTC and monobutyltin oxide were positive as SOS inducers (Hamasaki et al., 1992) and induced gene mutations in *Salmonella* Typhimurium strain TA100 without metabolic activation (Hamasaki et al., 1993). MBTC was negative in in vivo mouse micronucleus assays (Atochem NA, 1991a).

MOTC was negative in an Ames assay (Litton Bionetics Inc., 1979; Schering AG, 1979b), an HGPRT assay (Schering AG, 1989d) and an in vivo mouse micronucleus test (Schering AG, 1989e).

5.5 Reproductive and developmental toxicity

5.5.1 Tetrasubstituted compounds

In the reproductive/developmental toxicity segment of the OECD 422 study in rats for TeBT, adverse reproductive or developmental effects observed in the high-dose (2000 mg/kg diet) group (LOAEL; equivalent to 100–118 mg/kg bw/day for both sexes) included decreased number of pups, increased pup mortality, decreased pup body weight, increased number of runts and increased post-implantation loss. The NOAEL for maternal and reproductive/developmental toxicity for TeBT was 300 mg/kg diet (equivalent to 16–24 mg/kg bw/day) (Waalkens-Berendsen, 2004a). In a developmental gavage study in rats exposed on GDs 13–16, TeBT resulted in malformations (i.e. cleft palate) at ≥229 mg/kg bw/day; the result was significant only at 1833 mg/kg bw/day (Ema et al., 1996).

No adverse effects on fertility or reproductive performance and development were observed in the reproductive/developmental toxicity segment of the OECD 422 study in rats for TeOT, even at the highest (maternally toxic) dose tested of 7500 mg/kg diet. Based on the lack of observed effects, the NOAEL for reproductive/developmental toxicity of TeOT was 7500 mg/kg diet (445–480 mg/kg bw/day for males and 426–624 mg/kg bw/day for females) (Waalkens-Berendsen, 2004b).

No adverse effects on fertility or reproductive performance or development were observed in the reproductive/developmental toxicity segment of the OECD 422 study in rats for TePT. The NOAEL for reproductive/developmental toxicity was 500 mg/kg bw/day (the highest dose) (MHLW, 2008).

5.5.2 Trisubstituted compounds

In a two-generation reproduction study in rats administered TBTC at 0, 5, 25 or 125 mg/kg diet, a NOAEL could not be established because of the dose-related decrease in testis weight in male pups and increase of anogenital distance in female pups at all dose levels. The LOAEL was 5 mg/kg diet (0.25 mg/kg bw/day), based on decreased testis weight in F_1 adults and increased anogenital distance in pups (Ogata et al., 2001; Omura et al., 2001).

In a two-generation reproduction study in which rats were fed TBTO at 0, 0.5, 5.0 or 50 mg/kg diet (0, 0.02, 0.29 or 2.95 mg/kg bw/day for F_0 males and 0, 0.03, 0.34 or 3.43 mg/kg bw/day for F_0 females), the NOAEL for adult toxicity was 0.29 mg/kg bw/day, based on decreased thymus weight, and the NOAEL for reproductive/developmental toxicity was 0.34 mg/kg bw/day, based on decreased pup body weight during lactation (Schroeder, 1990).

In a developmental study in which pregnant CD rats were gavaged daily with TBTC at 0, 0.025, 0.25 or 2.5 mg/kg bw/day from GD 8 until weaning, when pups were gavaged daily up to PND 30, 60 or 90 with the same dose of TBTC administered to their mothers, all doses of TBTC significantly affected parameters of the growth profile of the pups and decreased feed conversion in males. At the high dose, reduced serum thyroxine levels in male pups were evident, indicating that the thyroid is a target for TBTC toxicity. Significant decreases in liver weights were seen in the top two dose groups, but no histopathological lesions were observed. Decreases in spleen and thymus weights were observed at the top dose. The maternal NOAEL was 0.025 mg/kg/day, based on heart and lung effects at 0.25 mg/kg bw/day (Cooke et al., 2004).

In several oral studies, maternal exposure of rats to TBTC during early pregnancy caused embryo lethality and suppression of fetal body weights at maternally toxic doses. Depending on the dose and period of exposure, a few studies resulted in malformations (generally cleft palate) in offspring (OECD, 2010). The NOAEL for maternal toxicity was 5 mg/kg bw/day in dams exposed on GDs 7–15 (Itami et al., 1990). In another study, the NOAEL for maternal toxicity was 8 mg/kg bw/day when dams were exposed on GDs 0–7 (Harazono, Ema & Ogawa, 1996). The LOAEL for developmental toxicity was 25 mg/kg bw/day in offspring exposed during GDs 13–15, due to increased incidence of cleft palate (Ema et al., 1995). The LOAEL for developmental effects in offspring when dams were exposed from GD 7 to GD 15 was 5 mg/kg bw/day, based on a decreased number of ossified sternebrae (variation) (Itami et al., 1990). The LOAEL for developmental toxicity was 0.25 mg/kg bw/day in offspring exposed during GDs 0–19, due to increased mean anogenital distance in males (Adeeko et al., 2003).

In a developmental toxicity study in which rats were treated with TBTO by gavage at doses of 0, 5, 9 or 18 mg/kg bw/day on GDs 6–19, the LOAEL for maternal toxicity was 5 mg/kg bw/day, based on decreased body weight gain, and the LOAEL for developmental toxicity was 5 mg/kg bw/day, based on increased incidences in all dose groups of minor anomalies of the axial skeleton, particularly asymmetric sternebrae, rudimentary ribs and 14th rib pair (Schroeder, 1981). In another developmental toxicity study in rats exposed to TBTO by gavage (0, 2.5, 5.0, 10, 12 or 16 mg/kg bw/day on GDs 6–20), maternal body weight gain was significantly reduced and maternal mortality was increased at 10 mg/kg bw/day and above. The NOAEL for developmental toxicity was 5.0 mg/kg bw/day, based on decreased litter size, pup survival rates, pup body weights, weights of pup brain tissues, motor activity and delay in age of vaginal opening (Crofton et al., 1989). In mice treated with TBTO by gavage at 0, 1.2, 3.5, 5.8, 11.7, 23.4 or 35.0 mg/kg bw/day on GDs 6–15, the NOAEL for maternal and developmental toxicity was 5.8 mg/kg bw/day, based on reduced body weight gain in dams and increased cleft palate in fetuses (Davis et al., 1987).

In a developmental toxicity study in which rabbits were given TPTOH by gavage on GDs 6–18, the NOAEL for maternal toxicity was 0.1 mg/kg bw/day, based on reduced weight gain, and the NOAEL for fetal toxicity was 0.3 mg/kg bw/day, based on decreased fetal weight (Rodwell, 1987). When rats were given TPTOH by gavage on GDs 6–15, the NOAEL for maternal toxicity was 1.0 mg/kg bw/day, based on reduced weight gain and feed consumption, and the NOAEL for embryotoxicity was 2.8 mg/kg bw/day, based on increased resorptions and reduced fetal weight (Rodwell, 1985). In a two-generation study in rats administered TPTOH, reduced litter size, weight gain, survival, and spleen and thymus weights were observed in rat pups at exposure levels not inducing toxicity in adults. The NOAEL was 0.4 mg/kg bw/day, based on decreased litter size, pup weight, and relative spleen and thymus weights in weanlings (Young, 1986).

5.5.3 Disubstituted compounds

Pregnant rats were given DMTC by gavage at 0, 5, 10, 15 or 20 mg/kg bw/day on GDs 7–17. The LOAEL for maternal and fetal effects was 15 mg/kg bw/day, based on lower body weight gain, reduced thymus weight in dams and reduced fetal weights (Noda, 2001). In a second experiment in the same report, rats were given DMTC at 20 or 40 mg/kg bw/day at GDs 7–9, 10–12, 13–15 or 16–17. Cleft palate was not seen at either dose level after any of the exposure periods. Numbers of fetuses with skeletal variation, cervical ribs and/or splitting of the first cervical vertebral arch increased significantly in the 40 mg/kg bw/day group dosed on GDs 7–9 or 13–15 (Noda, 2001).

Pregnant rats were given DBTC by gavage at 0, 3.8, 7.6 or 15.2 mg/kg bw/day on GDs 0–3. Decreased body weight gain in female rats, and an increase in implantation failure and preimplantation embryonic loss were found at 7.6 mg/kg bw/day and higher (Ema & Harazono, 2000). Decreased serum progesterone levels following administration of DBTC in pseudopregnant rats suggested that a decline in progesterone levels caused the failure of implantation (Harazono & Ema, 2003).

DBTC was given to pregnant rats by gavage at 0, 2.5, 5.0, 7.5 or 10.0 mg/kg bw/day on GDs 7–15. Maternal toxicity, decreases in body weight gain and decreases in feed consumption were observed at 7.5 mg/kg bw/day and higher. An increase in the incidence of fetuses with malformations, such as cleft jaw, ankyloglossia, defect of the mandible, fusion of the ribs and deformity of the vertebral column, was found at 5.0 mg/kg bw/day and higher. The NOAELs for maternal and developmental toxicity were 5.0 and 2.5 mg/kg bw/day, respectively (Ema, Itami & Kawasaki, 1991). In contrast, Farr et al. (2001) observed maternal toxicity, including decreased feed consumption, body weight gain and thymus weight, but no significant increase in the incidence of fetuses with malformations, at 10.0 mg/kg bw/day in rats administered DBTC by gavage at 0, 1.0, 2.5, 5.0 or 10.0 mg/kg bw/day on GDs 6–15.

When DBTC was administered during GDs 6–17 or 7–15, maternal toxicity and increased preimplantation, but not post-implantation, losses were observed. The adverse effects varied with the gestational stage at the time of maternal exposure; developmental effects were seen when DBTC was administered on GD 7 or 8, but not on GDs 0–3, 4–7, 13–15, 6 or 9 (Noda et al., 1992a).

In a reproductive/developmental toxicity screening test in rats administered DBTC at 0, 5, 30 or 200 mg/kg diet, the NOAEL for general toxicity was 5 mg/kg diet (0.3 and 0.4 mg/kg bw/day for males and females, respectively), based on reductions in body and thymus weights, and thymic lymphoid depletion. The NOAEL for reproductive toxicity was 1.7–2.4 mg/kg bw/day, based on decreases in pup body weights, live pups per litter, live birth index, females surviving delivery and females with liveborn pups; and increases in post-implantation loss, number of runts, pup mortality, stillborn pups and number of pregnant females that did not deliver (Waalkens-Berendsen, 2003).

When pregnant rats were treated orally with DBTA at 0, 1.7, 5.0 or 15 mg/kg bw/day on GDs 0–19, decreased thymus weight in dams and an increased incidence of fetuses with malformations, such as mandible dysplasia, ankyloglossia and schistoglossia, were detected at 15 mg/kg bw/day (Noda et al., 1988).

After administration of DBTC, DBTA, DBT maleate, DBTO or DBT dilaurate to rats by gavage on GD 8, no differences in the types of developmental toxicity were noted between the five DBT compounds. This suggests that the dibutyl group, rather than the anionic group, is important in the developmental toxicity of DBTs (Noda, Morita & Baba, 1993).

In an extended one-generation reproductive toxicity study, parental rats were exposed to DOTC via the feed (0, 3, 10 or 30 mg/kg diet) during premating, mating, gestation and lactation, and subsequently F_1 offspring were exposed from weaning until sacrifice. No adverse effects on parental animals, including systemic effects, or effects on fertility or reproductive performance, were found at any dose. At the high dose (1.7–2.1 mg/kg bw/day during gestation and 2.9–5.2 mg/kg bw/day during lactation), individual pup mortality at PND 4 was statistically significantly increased; male pup weights were significantly increased on PNDs 8, 10 and 13;

and absolute and relative thymus weight and thymus cellularity were decreased on PND 42. The immunotoxicity end-points examined are described in section 5.6.3 (Tonk et al., 2011a).

In a study in which rats were exposed to DOTC by gavage from PND 10 to PND 21 (0, 0.15, 0.3, 0.5, 1.0, 1.5, 3.0 or 5.0 mg/kg bw/day) and via the diet after weaning (0, 3, 6, 10, 20, 30, 60 or 100 mg/kg feed) until time of sacrifice, effects included a dose-dependent decrease in F_1 body weight, a dose-dependent increase in absolute and relative liver weights, a dose-dependent decrease in absolute and relative thymus weights, a decrease in thymus cellularity and relative thymic cell count at all time points evaluated, and a dose-dependent decrease in absolute and relative spleen weights and spleen cellularity. The immunotoxicity end-points examined are described in section 5.6.3 (Tonk et al., 2011b).

A developmental neurotoxicity study in pregnant rats dosed orally with DBTC (0, 2.5 or 5 mg/kg bw, 3 days per week) from GD 6 through weaning is described in section 5.7.

5.5.4 Mixtures of disubstituted and monosubstituted compounds

Satellite groups to assess reproductive and developmental toxicity were included in a 90-day oral rat study using a mixture of MBTC and DBTC (99.72%:0.21%) (see section 5.2.4). Four groups (0, 300, 1500 or 7500 mg/kg diet) of female rats were mated with treated males from the main 13-week study. Females received the treated diets beginning 2 weeks before mating, through mating and gestation, and up to PND 4. The NOAELs for MBTC for maternal toxicity, fertility and developmental effects were 521 and 433–685 mg/kg bw/day for males and females, respectively (Appel & Waalkens-Berendsen, 2004b).

In a two-generation reproductive toxicity study, rats were fed diets containing an 80%:20% mixture of dioctyltin diisothioglycolate (DOTTG) and monooctyltin triisooctylthioglycolate (MOTTG) at 0, 20, 60 or 200 mg/kg (0, 1.9, 5.4 or 17.1 mg/kg bw/day). The NOAEL was 20 mg/kg feed (1.9 mg/kg bw/day for the mixture; 1.5 mg/kg bw/day for DOTTG), based on thymus effects (Mitterer, 1997). A study in rats dosed on GDs 6–15 with the same 80:20 mixture of DOTTG and MOTTG at 0, 1, 5 or 25 mg/kg bw/day showed significant embryotoxicity at 25 mg/kg bw/day. The NOAEL was 5 mg/kg bw/day (Battenfeld, 1991). A comparable study on rabbits (dosed on GDs 6–18 at DOTTG and MOTTG of 0, 1, 10 or 100 mg/kg bw/day) showed marginal effects on fetal development at 10 mg/kg bw and significant embryotoxicity and embryolethality at 100 mg/kg bw. The NOAEL was 1 mg/kg bw/day (Battenfeld, 1992).

In a study of a mixture of 80% DOTTG and 20% MOTTG administered by gavage to mice at 0, 20, 30, 45, 67 or 100 mg/kg bw/day on GDs 6–17, Faqi, Schweinfurth & Chahoud (2001) observed an increased incidence of embryonic resorptions, fetuses with cleft palate and reduced fetal weight at 67 mg/kg bw/day and higher. Decreased weights of the liver and thymus in dams, and increased incidence of fetuses with exencephaly were seen at 100 mg/kg bw/day. The NOAEL for malformations was 45 mg/kg bw/day; no NOAEL was identified for skeletal anomalies because of supernumerary lumbar ribs observed at all doses. The maternal NOAEL was 30 mg/kg bw/day.

Ciba-Geigy Ltd (1983c) found no treatment-related developmental effects after dosing rats by gavage with a mixture of MOTTG and DOTTG (67%:33%) at 0, 20, 60 or 120 mg/kg bw/day during GDs 6–15. The NOAEL was 120 mg/kg bw/day, the highest dose tested.

Satellite groups to assess reproductive and developmental toxicity were included in a 90-day oral rat study using a DOTC:MOTC (94.09%:2.25%) mixture (see section 5.2.4). Four groups (0, 10, 100 or 300 mg/kg diet; 0, 0.5–0.7, 4.2–5.9 or 8.40–17.0 mg/kg bw/day) of female rats were mated with treated males from the main 13-week study. Females received the treated diets beginning 2 weeks before mating, through mating and gestation, and up to PND 4. The NOAEL for DOTC for fertility and developmental effects was 0.5–0.7 mg/kg bw/day, based on decreases in gestation, live birth and viability indices; and increases in post-implantation loss, number of runts, number of stillborns and pup mortality on PND 1–4. Based on the thymic lymphoid depletion in DOTC-treated dams, the LOAEL for maternal toxicity was 0.5–0.7 mg/kg bw/day (Appel & Waalkens-Berendsen, 2004c).

Satellite groups to assess reproductive/developmental toxicity were included in a 90-day oral rat study using an MOTC:DOTC (89:11) mixture. Four groups (0, 10, 100 and 500 mg/kg diet; 0, 0.5–0.7, 4.8–7.7 and 22.3–33.0 mg/kg bw/day) of female rats were mated with treated males from the main 13-week study. Females received the treated diets beginning 2 weeks before mating, through mating and gestation, and up to PND 4. The NOAEL for MOTC for maternal toxicity was 0.5–0.7 mg/kg bw/day, based on severe thymic atrophy and decreased thymic weights. The NOAEL for MOTC for fertility and developmental effects was 4.8–7.7 mg/kg bw/day, based on decreased number of liveborn pups, increased number of stillborn pups, increased pup mortality on PND 4, increased post-implantation loss, decreased gestation, decreased live birth index and decreased viability index (Appel & Waalkens-Berendsen, 2004d).

5.5.5 Monosubstituted compounds

A reproductive/developmental screening study in rats was conducted using MMTC at doses of 0, 30, 150 or 750 mg/kg diet (0, 1.5, 7.5 or 37.5 mg/kg bw/day) over 8 weeks. Treatment-related maternal effects (decreased body weight), and effects on reproduction and development of the pups (increased post-implantation loss and mortality, decreased viability index and number of live pups) were observed at the highest dose. The NOAEL for fertility and developmental effects, and maternal toxicity was 7.5 mg/kg bw/day (Appel & Waalkens-Berendsen, 2004c).

In the full gestational study of rats orally administered MBTC (0, 50, 100, 200 or 400 mg/kg bw/day) during GDs 7–17, no maternal toxicity or thymic atrophy was reported, and no dose-dependent developmental toxicity was evident on GD 20 (Noda et al., 1992b). In rats administered MBTC (0, 1000, 1500 or 2000 mg/kg bw) via gavage on GDs 7 and 8, maternal deaths were significantly increased at 1500 and 2000 mg/kg bw, and maternal body weight gain was significantly decreased at 1000 and 1500 mg/kg bw. However, no external malformations were found in the fetuses (Ema et al., 1995). Ema & Harazono (2001) treated rats orally with MBTC (0, 56, 226 or 903 mg/kg bw/day) during GDs 0–3 or 4–7; decreased maternal body weight gain, decreased feed consumption and decreased pup body weights were found at 903 mg/kg bw/day, but not at 56 or 226 mg/kg bw/day.

5.6 Immunological effects

5.6.1 Tetrasubstituted compounds

Decreased thymic weights with lymphoid depletion after TeBT and TeOT exposure of rats were observed in the combined repeated-dose and reproductive/developmental toxicity screening test (OECD TG 422) at doses of approximately 300 mg/kg bw/day and above

(Waalkens-Berendsen 2004a,b). Conversely, no adverse effects on these end-points were observed at the highest dose (500 mg/kg bw/day) of TePT in a combined repeated-dose and reproductive/developmental toxicity screening test (OECD TG 422) (MHLW, 2008).

5.6.2 Trisubstituted compounds

The immunotoxicity of TBTO and TPT is apparent from the thymus atrophy and related downstream lesions in various toxicity studies described above (Til, Feron & de Groot, 1970; Krajnc et al., 1984; Young, 1986; Schroeder, 1990).

Rats fed for up to 6 weeks with TBTO at 0, 20 or 80 mg/kg diet (0, 1 or 4 mg/kg bw/day) showed suppression of delayed-type hypersensitivity responses, antibody responses, resistance to *Trichinella spiralis* infection, and the viability and mitogenic response to phytohaemagglutinin and concanavalin A, but not to pokeweed mitogen or lipopolysaccharide, in spleen cells. No NOAEL was established (Vos et al., 1984a; Vos, Krajnc & Wester, 1985).

A similar set of parameters was assessed in male rats exposed to TBTO at 0, 0.5, 5 or 50 mg/kg diet (0, 0.025, 0.25 or 2.5 mg/kg bw/day) for 4–6 and 15–17 months. Resistance to *T. spiralis* was apparent at 0.25 mg/kg bw/day (based on immunoglobulin E titres, larvae count and inflammatory reaction). There were no major differences in the effects between the animals tested at 4–6 and 15–17 months. A NOAEL of 0.025 mg/kg bw/day was identified (Vos et al., 1990).[1]

In the developmental study reported by Cooke et al. (2004) (see section 5.5.2), detailed examinations of immune functions following exposure of rats to TBTC (0, 0.025, 0.25 or 2.5 mg/kg bw/day) revealed increased natural killer cell numbers at 2.5 mg/kg bw/day and a nonlinear dose–response increase in natural killer cell activity at all doses. Other changes included an increase in IgM levels at the low and high doses, and in IgG levels at the middle and high doses; an increased mean percentage of CD4(+)8(+) (immature) T-lymphocytes at the middle and high doses; increased mean numbers of *Listeria monocytogenes* colony-forming bacteria on day 2 post-infection at all dose levels, and on day 3 only at the middle dose; an increased delayed-type hypersensitivity response to oxazolone at the low and middle doses; and a decreased delayed-type hypersensitivity response in high-dose males at 90 days. There was a clear NOAEL of 0.025 mg/kg bw/day for functional immune response (host defence reaction against *Listeria*) (Tryphonas et al., 2004).

Immunotoxicity studies have been conducted with TPT in rats, mice and guinea-pigs. In male rats fed TPTOH at 0, 5, 25 or 100 mg/kg diet (0, 0.25, 1.25 or 5 mg/kg bw/day) for 3 weeks, blood lymphocytes and eosinophils were significantly decreased at 0.25 mg/kg bw/day. Thymus weight, delayed type hypersensitivity and the mitogen response in spleen cells were reduced at 1.25 mg/kg bw/day. The LOAEL was 0.25 mg/kg bw/day (Vos et al., 1983, 1984b). In male rats exposed to TPTC at 0, 15, 50 or 150 mg/kg diet (0, 0.75, 2.5 or 7.5 mg/kg bw/day) for 2 weeks, thymus weight was reduced at all doses, and spleen weight was reduced in a dose-dependent fashion (Snoeij et al., 1985). In a study of mice given TPTOH at 0, 1, 5, 25, 50 or 125 mg/kg diet (0, 0.15, 0.75, 3.75, 7.5 or 18.75 mg/kg bw/day) for 28 days, various signs of immunotoxicity were seen at the higher doses, including weight reduction of spleen and thymus, and reduction in white blood cell counts, B-cells in spleen, T-cells in thymus and

[1] Based on this study, the United States Environmental Protection Agency calculated a lower 95% confidence limit on the benchmark dose for a 10% response ($BMDL_{10}$) of 0.03 mg/kg bw/day (US EPA, 1997).

immunoglobulins. The NOAEL was 0.75 mg/kg bw/day (McCormick & Thomas, 1990). TPTA in the diet of guinea-pigs (15 mg/kg diet; 1.5 mg/kg bw/day) decreased thymus weight and the number of plasma cells of the spleen and lymph nodes in females examined on days 47 and 77. After 104 days, the immunological reaction against tetanus toxoid was inhibited as a result of a lower antibody count and decreased antitoxoid-producing cells in the popliteal gland (Verschuuren et al., 1970).

5.6.3 Disubstituted compounds

Arakawa & Wada (1993) dosed rats with DMT for 10 days at 5 mg/kg bw/day and reported no atrophic effects on the thymus. Similar studies with DMT showed no effects on the lymphoid organs (Seinen et al., 1977a).

In short- or long-term and reproductive/developmental studies with DBT and DOT (e.g. Hennighausen & Lange, 1979, 1980; Penninks & Seinen, 1982; Miller & Scott, 1985; Noda et al., 1988; Volsen et al., 1989; Waalkens-Berendsen, 2003; Appel & Waalkens-Berendsen, 2004c, Kishi et al., 2006), thymic atrophy, lymphoid depletion and splenic depletion of the periarteriolar lymphocyte sheath were observed.

DBTC administered to rats at 50 or 150 mg/kg diet (2.5 or 7.5 mg/kg bw/day) resulted in immune suppression; effects were more pronounced with treatment during the developmental phase of the lymphoid system. Postnatal intubation of 5 mg/kg bw/day resulted in mortality, reduced growth and severe atrophy of lymphoid organs in rats. The LOAEL for DBTC in this study was 2.5 mg/kg bw/day. Altered immune functions were not observed in mice or guinea-pigs exposed via the diet to DBTC at 2.5 or 7.5 mg/kg bw/day (Seinen et al., 1977b).

In a series of immunotoxicity studies, thymic atrophy in rats was caused by exposure to DOTC at 50 mg/kg diet (2.5 mg/kg bw). Thymus-dependent immune suppression, decreased delayed-type hypersensitivity response (50 and 150 mg/kg diet), retarded rejection of skin transplants (150 mg/kg diet) and decreased graft-versus-host response (50 and 150 mg/kg diet) were observed, whereas thymus-independent humoral immune response and macrophage function were unaffected. Such effects were absent in mice and guinea-pigs (Seinen & Willems, 1976; Seinen et al., 1977a,b, 1979). When rats were exposed to DOTC prenatally, postnatally or both by oral gavage of pregnant and/or lactating females, no consistent alteration in immune function in offspring was observed. However, direct oral dosing of rat pups with DOTC at 5–15 mg/kg diet, beginning at 3 days of age and then 3 times per week up to 24 days of age for a total of 10 doses, resulted in significant suppression of the lymphoproliferative response of splenocytes to a T-cell mitogen in 10-week-old rats. These results suggest that direct dosing of pups during early postnatal life may be the most effective means of inducing immunosuppression with DOTC during immune system development (Smialowicz et al., 1988).

In an extended one-generation reproductive toxicity study, parental rats were exposed to DOTC via the feed (0, 3, 10 or 30 mg/kg diet) during premating, mating, gestation and lactation, and subsequently F_1 offspring were exposed from weaning until sacrifice. The T-cell–dependent antibody response to keyhole limpet haemocyanin (KLH) was evaluated on PNDs 21 and 35, and the delayed-type hypersensitivity response against KLH was evaluated on PND 49. No effects were found on PND 21. Effects on lymphocyte subpopulations in the thymus and spleen were observed only at 30 mg/kg diet on PNDs 42 and 70 (spleen only). The delayed-type hypersensitivity response showed an effect at 3 mg/kg diet and was the overall critical end-point (Tonk et al., 2011a). When rats were exposed to DOTC by gavage (0, 0.15, 0.3, 0.5, 1.0, 1.5, 3.0 or 5.0 mg/kg bw/day) from PND 10 to PND 21 and via the diet (0, 3, 6, 10, 20, 30, 60

or 100 mg/kg feed) after weaning until time of sacrifice, immune effects were more pronounced on PNDs 21 and 42 than on PND 70 and were observed at lower doses than developmental effects. The most sensitive immune parameters affected included T-cell–dependent antibody response parameters and thymocyte subpopulations. The KLH-stimulated lymphoproliferative response showed a dose-dependent increase, with a benchmark dose (BMD) of 0.29 mg/kg bw/day (90% CI 0.06–1.6 mg/kg bw/day) (Tonk et al., 2011b).

Female rats were exposed to DOTC at doses of 0, 3, 10 or 30 mg/kg feed (0, 0.57, 1.78 or 5.31 mg/kg bw/day) during pregnancy and up to 20 days (at weaning) or 56 days after delivery (Menke et al., 2012). Thymus weight was decreased, thymus morphology was affected, and the numbers of neutrophils were decreased in the lactating rats (PND 20) at 1.78 mg/kg bw/day and higher. These effects were no longer apparent at day 56, despite continuous exposure to DOTC. In age-matched non-mated females exposed to DOTC at 0, 3, 10 or 30 mg/kg feed (0, 0.19, 0.62 or 1.61 mg/kg bw/day) during the same time periods, these effects were not observed (Menke et al., 2012).

5.6.4 Mixtures of disubstituted and monosubstituted compounds

In several studies involving 3 months of feeding of mixtures of MOT:DOT, significant reductions in thymus weight were observed (Rohm and Haas, 1976; TNO, 1976; Ciba-Geigy Ltd, 1981). It was not clear whether this effect was due to the monosubstituted or disubstituted component of the mixture.

5.6.5 Monosubstituted compounds

Arakawa & Wada (1993) dosed rats with MMT for 10 days at 5 mg/kg bw/day and reported no atrophic effects on the thymus. Similar studies using MOT showed no effects on the lymphoid organs (Seinen et al., 1977a).

5.7 Neurotoxicity

TMT and TET are well-known potent neurotoxins, but they target different organs. TET primarily targets myelin sheaths and causes interstitial oedema throughout the white matter of the central nervous system, particularly the brain. TMT also causes severe damage to the central nervous system; however, the effect is neuronal necrosis rather than oedema (Krinke 2000a,b). TPT also has neurotoxic potential (Wu, Chang & Chiu, 1990; Lin et al., 1998). Other trialkyltins and dialkyltins are less neurotoxic or possibly not neurotoxic at all. There is a lack of systematic experimental data in the open literature comparing the in vivo neurotoxicity of organotin copounds. However, there are some indications of neurobehavioural effects. Definitive NOAELs cannot be derived from the studies currently available.

In two repeated-dose oral studies of mixtures of DMTC and MMTC (90%:10% and 63.5%:33.5%, respectively) (see section 5.2.4), consistent neurotoxicity results (behavioural and histopathological changes) were noted. A NOAEL of 0.98 mg/kg bw/day in the feeding study (ClinTrials BioResearch, 1997) and a LOAEL of 1.6–2.2 mg/kg bw/day in the drinking-water study (TNO, 1999) were obtained.

To evaluate neurotoxicity following developmental exposure to DMT, female rats were exposed to DMT (97% purity) in their drinking-water at concentrations of 0, 3, 15 or 74 mg/L (0, 1.6, 8.1 or 40 mg/L as Sn) for 2 weeks before mating, and through gestation and lactation (experiment 1), or to the same concentrations beginning at GD 6 and continuing through lactation (experiment 2). The results of both studies demonstrate a reproducible effect on

spatial learning of 15 ppm (1–3 mg/kg bw/day) perinatal DMT exposure. Changes in expression of apoptosis, brain weight and the occurrence of neuropathological lesions also indicate potential neurotoxicity of DMT (Ehman et al., 2007).

Developmental neurotoxicity was evaluated in pregnant rats dosed orally with DBTC (0, 2.5 or 5 mg/kg bw, 3 days per week) from GD 6 through weaning (Jenkins, Ehman & Barone, 2004). In exposed offspring, the incidence of apoptotic cell death, measured by DNA fragmentation and TUNEL staining, was increased in the neocortex and hippocampus on PND 38, but not at other ages examined. This study demonstrated that DBTC is neurotoxic in vitro (0.1 µM or 30.38 ng/mL, based on a 61% decrease in PC12 cell neurite outgrowth) at concentrations similar to, or lower than, those detected in human blood samples (12–94 ng/mL) (Whalen, Loganathan & Kannan, 1999). As well, DBTC in vivo caused apoptotic cell death in the neocortex and hippocampus in offspring.

MMTC provided to female rats in drinking-water at 12, 40 or 120 mg/L induced significant increases in the extinction of learning ability in pups at 11 days. At 120mg/L, the pups also displayed significantly increased acquisition time for learning. At 21 days, the pups had higher escape times than the controls at 12 and 120 mg/L but not at 40 mg/L (Noland, Taylor & Bull, 1982). To evaluate neurotoxicity following developmental exposure to MMT, female rats were exposed to MMT (97% purity) in their drinking-water at concentrations of 0, 10, 50 or 245 mg/L (0, 5, 25 or 120 mg/L as Sn) for 2 weeks before mating, and through gestation and lactation (experiment 1), or to 0 or 500 mg/L (245 mg/L as Sn) beginning at GD 6 and continuing through lactation (experiment 2). Neurobehavioural assessments (i.e. runway test, motor activity habituation and Morris water maze [as adults]) were made on the offspring. There were few treatment-related effects in the offspring perinatally exposed to MMT during gestation and lactation. At 500 mg/L (56–94 mg/kg bw/day), there was decreased water intake and a marginal trend towards decreased brain weight ($P < 0.07$). No effects on growth measures, development, cognitive function or apoptosis were found. The incidence of neuropathological lesions (i.e. vacuolation of neurophils in a focal area of the cerebral cortex) in the brains of MMT-exposed offspring evaluated as adults was minimal, using 1–3 rats per dose. The myelin and brain weights were unaffected. The authors concluded that perinatal exposure to MMT does not result in significant neurobehavioural or cognitive deficits. The biological significance of the mild neuropathological lesions observed in the adult offspring is unclear (Moser et al., 2006).

In a study in which rats were orally administered TBTC at 1 or 5 mg/kg bw/day during GDs 6–20, offspring showed clear evidence of alterations of behaviour in adulthood, such as a general hyperactivity, dysfunction of spatial learning performance and a drastic potentiation of the stimulating effects of d-amphetamine. No neurochemical correlation for these observations was found, as neurohistological changes were not investigated (Gardlund et al., 1991). In the maze learning test, male rats orally administered Tinestan at doses of 0.6 (0.36 mg/kg bw/day as TPTA) or 6 mg/kg bw/day, 6 days/week for 6 weeks seemed to make many mistakes and showed slow reaction speed. In the conditioned avoidance response test, no difference was observed between the treated and control groups. However, extinction of behaviour was delayed in the high-dose group after the stimulus was discontinued. Tin levels increased in the brain tissues, but no neurohistological signs were noted (Lehotzky et al., 1982).

5.8 Mode of action

Immunotoxicity is the critical end-point for disubstituted and trisubstituted organotin compounds. DBT, DOT, TBT and TPT are known to induce thymic atrophy. The finding that

TBT is about 40% less potent than DBT in reducing relative thymus weight may be explained by the lower activity of TBT or the induction of thymic atrophy by the metabolite DBT rather than by TBT itself (Snoeij, Penninks & Seinen, 1988). Side-chain length is important in determining immunotoxicity. DMT did not reduce thymus weight, and diethyltin only slightly reduced thymus weight, whereas didodecyltin and dioctadecyltin were ineffective in reducing thymus weight (Seinen et al., 1977a; Snoeij, Penninks & Seinen, 1987). TBT and TPT both exert significant immunotoxicity in rats (Krajnc et al., 1984; Vos et al., 1984b; Snoeij et al., 1985), mice (Boyer, 1989; Nishida et al., 1990) and guinea-pigs (Verschuuren et al., 1966, 1970), whereas trihexyltin and trioctyltin congeners exhibit limited or no immunotoxicity. In vitro cytotoxicity and in vivo immunotoxicity of the organotins are well correlated (Brüschweiler, Würgler & Fent, 1995). Immunosuppressive effects appear to be due primarily to the induction of programmed cell death in immunocompetent cells. Although Gennari et al. (1997) proposed that apoptosis induced in vitro was not relevant for thymus atrophy observed in vivo, in vivo cytopathological findings have demonstrated treatment-related increases in phagocytes with engulfed apoptotic thymocytes (Raffray & Cohen, 1993). This is supported by the observation of increased macrophage clearance activity in the thymus following administration of organotins (De Waal et al., 1993; Kempston et al., 1993; Raffray & Cohen, 1998), and histological studies demonstrating that the decrease in lymphoid organ weights was associated with a depletion of lymphocytes in the thymus, and thymus-dependent areas of the spleen and lymph nodes (Seinen & Willems, 1976; Penninks et al., 1985).

Dialkyltins, particularly DBT, display a strong affinity for dithiol groups and may interfere with receptor-dependent communication between intrathymic cells (Penninks & Seinen, 1983; Pieters, Bol & Seinen, 1994). Various findings considered together suggest that organotins may have an effect at the level of the cell membrane and/or cytoskeleton, resulting in disturbances of intercellular and intracellular communication processes. These processes are of crucial importance to thymocyte proliferation and differentiation in maturation (Pieters et al., 1993, 1995; Pieters, Bol & Penninks, 1994; Pieters, Bol & Seinen, 1994).

Although in vitro studies on DOT are rare, in vivo investigations suggest similar or comparable effects to the other organotin congeners (Miller et al., 1986; Smialowicz, 2002).

Recent studies have indicated that organotin compounds, including TBT and TPT, bind and activate both peroxisome proliferator–activated receptor (PPAR) and retinoid X receptor (RXR) (Kanayama et al., 2005; Nakanishi et al., 2005; Grün et al., 2006; Hiromori et al., 2009; Le Maire et al., 2009; Yanik et al., 2011). Prenatal TBT exposure increased adipose depot size in mice via activation of PPARγ (Grün et al., 2006) and reprogrammed the fate of multipotent mesenchymal stromal stem cells, both in vitro and in vivo (Kirchner et al., 2010; Chamorro-García et al. 2013). These studies suggested that organotin compounds could activate nuclear receptors as a common physiological molecular mechanism and may have potential for endocrine disruption. However, currently, there is no direct evidence that the activation of these receptors is associated with any endocrine disruption effects. Moreover, the activation of PPAR and RXR by DBT exposure is far less potent than that by TBT or TPT exposure, despite DBT having immunotoxicological potency similar to that of TBT. No interpretation has been reported of the relationship between these molecular events and the immunosuppressive effects and other adverse end-points of disubstituted and trisubstituted organotin compounds. Further investigations on the molecular mechanism of the adverse effects would be useful.

6 Practical considerations

6.1 Analytical methods and achievability

Many options are available for analysis of organotin compounds. Analysis usually comprises four steps: extraction; formation of volatile derivatives, when necessary; separation; and detection/quantification. The preferred separation technique has been gas chromatography, because of its high resolution and detector versatility, and, more recently, liquid chromatography.

Derivatization methods include formation of alkyl (methyl or pentyl) derivatives using a Grignard reagent, formation of ethyl derivatives using sodium tetraethylborate or formation of hydrides using sodium borohydride. Detection and quantification can be performed using a flame photometric detector, atomic absorption spectrometry or mass spectrometry (IPCS, 1990; Prange & Jantzen, 1995; Jiang, Xu & Zhang, 1999; Takeuchi, Mizuishi & Hobo, 2000; Liu, Jiang & Zhou, 2001; Boraiko et al., 2004) or microwave-induced and inductively coupled plasma atomic emission spectrometry (Tutschku, Mothes & Dittrich, 1994; Minganti, Capelli & Depellegrini, 1995).

The International Organization for Standardization (ISO, 2004) has a gas chromatographic method for determining certain organotin compounds in drinking-water, surface water and wastewater containing not more than 2 g/L of suspended material. The method involves derivatization with sodium tetraethylborate and liquid/liquid extraction in a working range of 10–1000 ng/L. The method is based on determination of the cation (e.g. MBT, DBT, TBT, TeBT, MOT, DOT, TPT), and the respective anions are not determined.

Inductively coupled plasma mass spectrometry was used to analyse six organotin compounds (chlorides of DMT, DBT, TMT, TBT, DPT and TPT). The detection limits for the six organotins were 24–51 pg as Sn; the dynamic range was more than 10^4, from 1 µg/L to 10 mg/L (Inoue & Kawabata, 1993).

High-performance liquid chromatography has also been used, the advantage being that no derivatization step is required. Most separations are based on ion exchange or reversed-phase gradient elutions. Atomic absorption spectrometry, inductively coupled plasma mass spectrometry and fluorometric detection can be used. High-performance liquid chromatography coupled with atomic absorption spectrometry is commonly used for the speciation of organotin compounds (Takeuchi, Mizuishi & Hobo, 2000).

Derivatization–liquid extraction followed by analysis by gas chromatography and mass spectrometry is highly sensitive and most applicable for analysing organotins in water (Ministry of Environment, Japan, 2002). Isotopic surrogates are first added to the samples, then extraction with *n*-hexane is employed after derivatization with sodium tetraethylborate. The extract solution is concentrated and cleaned up with florisil. The extract solution is further concentrated with nitrogen purge for gas chromatography and mass spectrometry–selective ion monitoring analysis. The detection limits are 0.2–0.4 ng/L for DBT, TBT, DPT and TPT, and 2 ng/L for MPT (Ministry of Environment, Japan, 2002).

EPA Method 8323 (US EPA, 2003) uses solid-phase extraction discs and micro-liquid chromatography coupled with mass spectrometry for determination of organotins (TBT, DBT, MBT, TPT, DPT and MPT as the cation) in water samples. The detection limits are given as 0.78, 0.97, 1 and 0.92 ng for TBT, DBT, MBT and TPT, respectively.

6.2 Treatment and control methods and performance

It is important to control both organotins that are present in the source water as environmental contaminants and organotins that leach from PVC piping.

Based on laboratory studies and knowledge from the operation of a full-scale treatment plant (Prasad & Schafran, 2006), treatment options for TBT removal were examined. They included physicochemical treatment processes of coagulation–clarification, filtration and granular activated carbon adsorption. Laboratory tests with aluminium sulfate and ferric sulfate showed that, on average, 90% of TBT in shipyard waters could be removed by coagulation–flocculation–clarification under optimal conditions.

Gao et al. (2009) compared organotin removal efficacies using conventional treatment (including flocculation, filtration and sodium hypochlorite disinfection) and an advanced treatment (including preoxidation, flotation, filtration, ozonation, activated carbon and chloramine disinfection) with solid-phase microextraction and analysis by gas chromatography and mass spectrometry. Removal ratios of organotins in conventional water treatment are not likely to be high, although available data and quantification information are still limited. DPT and TPT were not detected in drinking-water after advanced treatment processes, whereas removal of DPT and TPT using conventional treatment processes was only 17% and 7%, respectively. In contrast, the other organotin compounds were still present in drinking-water after the advanced treatment. Removal of MBT and DBT was 77% and 51%, respectively. This was lower than using conventional treatment processes (more than 95% for each). In addition, 43% of TBT and 69% of MPT were removed from raw water after the advanced treatment, similar to the removal rates using conventional treatment. The removal efficiency is significantly different for different compounds, although the reason is unknown. However, the sampling size in this study was small (six samplings over 2 years).

Treatment is generally not an effective approach to reduce the concentration of organotins (especially monoalkyltins and dialkyltins) in drinking-water that originates from plastic service water pipes and fittings, particularly PVC pipes and fittings. Recognizing this, use of organotins in PVC is very limited in most countries, as is the uptake of organotins from water. Daily intakes (assuming drinking-water consumption of 2 L/day) are likely to be very low – a few hundred nanograms per day at the most – which is less than the daily intake through food. For organotin stabilizers leached from PVC pipes and fittings, the most important means of control is by product specifications delivered through an appropriate certification scheme for materials in contact with drinking-water.

7 Conclusions

7.1 Summary of health effects

The critical end-point for the risk assessment of tri substituted and disubstituted compounds is immunotoxicity. Although TBT, TPT and DOT compounds induced tumours in various organs of experimental animals, the weight of evidence indicates that these organotins are not mutagenic. Reduced fecundity and developmental abnormalities are less sensitive end-points than immunotoxicity. In addition, neurotoxicity in humans has been reported for TMT and TET and, more recently, for TPT. However, causality cannot be established, and none of the reports contained sufficient information to characterize the exposure or any dose–response relationship.

As reported by EFSA (2004):

> [TBT, DBT, TPT and DOT] cause thymus atrophy with lymphocyte depletion in the thymus, spleen and peripheral lymphoid tissues, decreases in immunoglobulin concentrations, lymphopenia and decrease in white blood cells in rodents. As a result the thymus dependent immunity is depressed. These effects observed in rats have relevance for humans as *in vitro* studies with human thymocytes indicated that these cells are sensitive to [organotin compounds]. Furthermore, it is reasonable to assume that similar downstream effects can be expected for all those [organotin compounds] which typically affect the thymus since they all activate apoptotic mechanisms probably related to the occurrence of death receptors in the immune system. Based on [assumed] similar mode of action the effects of [organotin compounds] can be considered additive. Besides TBT and TPT this also applies for DBT and DOT compounds.

A NOAEL for TBTO of 0.025 mg/kg bw/day for immune parameters was identified in two chronic studies (Wester et al., 1988, 1990; Vos et al., 1990). TPTOH has a LOAEL for immunotoxic effects at the same order of magnitude as for TBTO. Although effects of chronic exposure to DBT are unknown, short-term experiments demonstrated that TBT-induced thymic atrophy is mediated by its metabolite, DBT, which suggests that DBT is at least as potent as TBT. In addition, in comparative toxicity studies, DBT and DOT were the most potent dialkyltin compounds, producing dose-related thymic atrophy to a similar extent. As these compounds – TBT, TPT, DBT and DOT – have a similar profile of action and potency in terms of immunotoxicity (lymphocyte depletion in the thymus and peripheral lymphoid tissues), a group TDI for TBT, TPT, DBT and DOT can be established, which would also protect against the other toxic effects. Although decreased thymic weights with lymphoid depletion were also reported following exposure to TeBT and TeOT in short-term studies, the corresponding LOAELs for TeBT and TeOT are two orders of magnitude higher than for trisubstituted and disubstituted compounds. Therefore, tetrasubstituted compounds were not included in the group TDI.

7.2 Derivation of the health-based value

In the absence of studies on combined effects, consideration of the immunotoxic effects of the organotin compounds (TBT, DBT, TPT and DOT) as additive is justified. Based on the chronic immunotoxicity studies in rats (Wester et al. 1988, 1990; Vos et al., 1990), a TDI of 0.25 µg/kg bw (0.1 µg/kg bw as Sn) was established. This involved applying an uncertainty factor of 100, to account for interspecies differences and intraspecies variability, to the lowest NOAEL for TBTO (the reference organotin for assessment of combined exposure to TBT, DBT, TPT and DOT) of 0.025 mg/kg bw/day. Allocating 20% of the group TDI of 0.25 µg/kg bw to drinking-water and assuming that a 60 kg person consumes 2 L of drinking-water per day, a health-based value (HBV) of 1.5 µg/L can be derived for the sum of TBT, TPT, DBT and DOT concentrations. Based on TBTO molecular mass, this group HBV is equivalent to 0.6 µg/L as Sn. Because intake of these organotin compounds is likely to be very low – typically less than a few hundred nanograms per day – there is no need to establish a formal guideline value (GV) for this group of organotin compounds. This implies that incorporation of these organotin compounds into national standards is usually unnecessary. However, the HBV provides guidance to Member States when there is a local concern.

Reliable lifetime TDI values for MMT, DMT and DMTC could not be derived because of a lack of long-term studies with systematic experimental data. The lowest definitive effects of MMT and DMT were observed at around 1 mg/kg bw/day in a 90-day repeated-dose study using a mixture of DMTC and MMTC. The presumed TDI for DMTC could be 10 or more times higher than that for immunotoxicity of TBTO. These organotins would normally be

found in drinking-water as a result of their use as stabilizers in PVC and CPVC. Accordingly, there is no need to establish a GV for these organotins because these uses are normally controlled by product specification.

For the other organotins (e.g. TMT, TeBT, MOT, TeOT, MPT, DPT, TePT), current knowledge is inadequate for setting an HBV or GV.

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